In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: March 27, 2019

TIA BUCCI *and* NICHOLAS BUCCI, *as parents of* D.B., *a minor*,	*	PUBLISHED
Petitioners,	*	No. 11-513V
v.	*	Special Master Gowen
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Hepatitis B (Hep B); Evans Syndrome; Immune Thrombocytopenia (ITP); Hemolytic Anemia; Bystander Activation.
Respondent.	*	

Lawrence R. Cohan, Anapol Weiss, Philadelphia, PA, for petitioners.
Robert P. Coleman, United States Department of Justice, Washington, DC, for respondent.

DECISION[1]

On August 11, 2011, Tia Bucci and Nicholas Bucci ("petitioners"), on behalf of their minor child, D.B., filed a petition in the National Vaccine Injury Compensation Program.[2] Petitioners allege that D.B. developed Evans syndrome which was caused in fact by a Hepatitis B ("Hep B") vaccination received on March 4, 2009. Based upon a full review of all of the evidence and testimony presented, I find that petitioners have not established that they are entitled to compensation.[3]

[1] In accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012), because this opinion contains a reasoned explanation for the action in this case, **this opinion will be posted on the website of the United States Court of Federal Claims**. This means the opinion will be available to anyone with access to the internet. As provided by 42 U.S.C. § 300aa-12(d)(4)B), however, the parties may object to the published Decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has 14 days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). **If neither party files a motion for redaction within 14 days, the entire opinion will be posted on the website and available to the public in its current form.** *Id.*

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to 34 (2012) (hereinafter "Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

[3] Pursuant to Section 300aa-13(a)(1), in order to reach my conclusion, I have considered the entire record including all of the medical records, statements, expert reports, and medical literature submitted by the parties. This opinion discusses the elements of the record I found most relevant to the outcome.

I. BACKGROUND

A. Procedural History

On August 11, 2011, petitioners filed their claim that D.B.'s March 4, 2009 hepatitis B vaccination was the cause-in-fact of his development of Evans syndrome. Petition (ECF No. 1). On October 31, 2011, respondent filed a Rule 4(c) Report recommending against compensation. Respondent's Report ("Resp. Rept.") (ECF No. 7). Respondent asserted that "Evans syndrome is an idiopathic illness with no known cause," petitioners had not yet submitted a report from a medical expert to establish that the Hepatitis B vaccine was the cause-in-fact of D.B.'s Evans syndrome, and "without the requisite medical opinion support," petitioners' claim would fail. *Id.* at 9.[4]

Subsequently, on December 9, 2011, petitioners filed one report from Dr. Marcel Kinsbourne. Petitioners' Exhibit ("Pet. Ex.") 3 (ECF No. 9).[5] On February 17, 2012, respondent filed the first report of Dr. Joan Cox Gill. Resp. Ex. A (ECF No. 13). Following a Rule 5 status conference on March 14, 2012, the special master assigned to the case directed the parties to jointly explore the potential for settlement of the case rather than proceeding in a litigation posture. Order (ECF No. 14). On September 20, 2012, petitioners filed the first report of Dr. Vera Byers. Pet. Ex. 7 (ECF No. 21).

The parties engaged in unfruitful settlement discussions until June 16, 2014, at which point they reached an impasse and requested an entitlement hearing, which the presiding special master agreed to set. Joint Status Report on June 16, 2014 (ECF No. 38); Scheduling Order on July 2, 2014 (ECF No. 39). Afterwards, the case was transferred to the undersigned. Order Reassigning Case on September 8, 2014 (ECF No. 42). On September 29, 2014, respondent filed the first report of Dr. Hayley Altman Gans. Resp. Ex. D (ECF No. 44). On March 27, 2015, petitioners filed the first report of Dr. Edwin Forman, Pet. Ex. 14, and Dr. Byers's second report, Pet. Ex. 16 (both at ECF No. 50). Both parties briefed the case prior to hearing.

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[4] As discussed below, Evans syndrome is a very rare condition, even by the standards of the Vaccine Program. However, it has been the subject of at least three prior claims. *See Isom v. Sec'y of Health & Human Servs.*, No. 97-770V, 1998 WL 835519 (Fed. Cl. Spec. Mstr. Nov. 3, 1998) (denying entitlement); *Cohen v. Sec'y of Health & Human Servs.*, No. 94-353V, 1998 WL 408784 (Fed. Cl. Spec. Mstr. July 1, 1998) (denying entitlement); *but see Mason v. Sec'y of Health & Human Servs.*, No. 14-487V, 2017 WL 3814643 (Fed. Cl. Spec. Mstr. Aug. 4, 2017) (approving the parties' stipulation awarding compensation to petitioners). These claims were before other special masters and did not involve the experts involved in the present claim. I have reviewed these past opinions on Evans syndrome, but I do not discuss them in this opinion because I reached my own independent conclusion based on the evidence submitted in this claim.

[5] Dr. Kinsbourne's primary specialty is neurology. His curriculum vitae lists some early experience with pediatrics but does not mention immunology, hematology, oncology, or blood disorders. Pet. Ex. 4 (ECF No. 9-2). His report does not address whether he is qualified to opine on these topics. Pet. Ex. 3. Petitioners' prehearing brief provides that they would rely in part on Dr. Kinsbourne's opinion. Pet. Prehearing Brief at 5. However, they do not provide any citations or specific points from the same. At the entitlement hearing, petitioners' counsel provided that they "chos[e] not to call Dr. Kinsbourne so as not to be repetitive." Tr. 4-5. Petitioners' posthearing brief does not cite to or reference any specific points from Dr. Kinsbourne. Thus, while I have reviewed and considered Dr. Kinsbourne's opinion in this case, it is not discussed in this opinion because I found it to be less relevant than the opinions of the other experts.

Petitioners' Prehearing Submission filed July 18, 2016 (ECF No. 70); Respondent's Prehearing Submission filed September 12, 2016 (ECF No. 76).

On November 1-2, 2016, an entitlement hearing was held in Washington, D.C. Petitioner Ms. Tia Bucci offered fact testimony. Petitioners presented expert testimony from Dr. Forman and Dr. Byers. Respondent presented expert testimony from Dr. Gans and Dr. Gill. During a post-hearing status conference, I set forth issues that the parties needed to address further in supplemental reports from Dr. Byers and Dr. Gans, as well as in their post-hearing briefs. I also encouraged further efforts at settlement. Post-Hearing Order on November 15, 2015 (ECF No. 85). On November 29, 2016, the entitlement hearing transcript was then entered on the docket. On December 16, 2016, petitioners filed Dr. Byers' third report. Pet. Ex. 27 (ECF No. 90). On January 17, 2017, respondent filed Dr. Gans's second report. Resp. Ex. W (ECF No. 92).

After the parties reengaged briefly in settlement discussions, on July 18, 2017, petitioners filed their post-hearing brief (ECF No. 106). On September 22, 2017, respondent filed his post-hearing brief (ECF No. 109).

Petitioners submitted a revised settlement demand to respondent. Joint Status Report on October 10, 2017 (ECF No. 110). They then reported that settlement was not feasible. Joint Status Report on November 13, 2017 (ECF No. 112). Due to the complexity of the case and involvement of an extremely rare condition, on June 12, 2018, I referred the parties to alternative dispute resolution. Order Referring to ADR on June 12, 2018 (ECF No. 119). However, they were unable to settle the case. Order Removing from ADR on October 18, 2018 (ECF No. 121). This matter is now ripe for adjudication.

B. Summary of Relevant Facts

1. Medical Records from Birth to the Hepatitis B Vaccination on March 3, 2009

D.B. was born at term, by cesarean section due to maternal hypertension and fetal distress, on August 27, 2008. Pet. Ex. 1 at 5, 1089. He received primary care at the PEDI Group Practice in Boston, Massachusetts. *Id.* at 1076. On September 4, 2008, at the one-week well child visit on September 4, 2008, Dr. Ronald Benz recorded that D.B. was a "[t]hriving baby." *Id.* at 1102. On September 16, 2008, at the two-week well child visit, Dr. Benz noted pus in D.B.'s eye and assessed him with conjunctivitis. *Id.* at 1097. On October 9, 2008, Dr. Benz assessed D.B. with oral thrush and an upper respiratory infection ("URI"). *Id.* at 1092-93. On October 20, 2008, at the two-month well child visit, D.B. was again assessed with thrush. *Id.* at 1091. At this same visit, D.B. received his first vaccinations for diphtheria-tetanus-acellular pertussis ("DTaP"), inactivated polio vaccine ("IPV"), hepatitis B ("hep B"), haemophilus influenzae type B ("Hib"), pneumococcal conjugate vaccine ("PCV7") and rotavirus. *Id.* Later that evening, D.B.'s mother brought him to the emergency department of Massachusetts General Hospital for complaints of irritability and discomfort. *Id.* at 2. D.B. was noted to be afebrile and was discharged home with instructions to take Tylenol for continued irritability. *Id.* at 5-6. D.B. received vaccinations without complication on December 17, 2008; January 7, 2009; and

February 18, 2009.[6]

2. Medical Records Postdating the Hepatitis B Vaccination on March 3, 2009

On March 4, 2009, D.B. returned to the pediatric practice to complete his six-month routine vaccination schedule. Pet Ex. 1 at 1074. At this visit, he received Hep B and Prevnar (PCV7) vaccinations at this visit. *Id.*

Three days post-vaccination, on March 7, 2009, D.B. and his mother returned to the pediatric practice. Pet. Ex. 1 at 1073. Dr. Hey Jin Chong recorded the mother's history that over the past few nights, D.B. had been waking up multiple times crying and tugging on his ear. *Id.* Dr. Chong observed that D.B. was afebrile and was not experiencing URI symptoms. *Id.* D.B. had normal ear canals with tympanic membranes clear and mobile. *Id.* at 1074. Thus, Dr. Chong ruled out ear infection. *Id.* at 1075. D.B. was not experiencing "excessive bleeding, bruising, [or] lymphadenopathy." *Id.* at 1074. However, he had a dime-sized bruise with induration on his right thigh, at the vaccination injection site. *Id.* Dr. Chong's assessment was "most likely pain/ irritability" following the vaccinations and directed his mother to give Tylenol and return to the clinic if D.B. developed a fever or URI symptoms. *Id.* at 1075.

Eleven days post-vaccination, on March 15, 2009, D.B. and his mother returned to the pediatric practice. Dr. Avram Traum recorded a history of "easy bruising over the past week, worse over last 2d. All over body, even with minor activity such as struggling in bath seat, grabbing at legs to pull up." Pet. Ex. 1 at 1071. Upon physical examination, Dr. Traum recorded that D.B. had "[i]nnumerable ecchymoses over head, pinnae, legs, arm. Petechiae noted as well"[7] and "epistaxis seen from left nares."[8] *Id.* at 1072. D.B. was referred to Massachusetts General Hospital for further evaluation. *Id.* at 729, 1072.

That same day, March 15, 2009, D.B. presented to the emergency room at Massachusetts General Hospital. The emergency department triage/ screening record provides that D.B.'s mother had observed both tiny red dots and bruises "this week." Pet. Ex. 1 at 11-12.

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[6] At his routine well-child visit on December 17, 2008, D.B. received DTaP, IPV, Hep B, and Rotavirus vaccinations. Pet. Ex. 1 at 1081. D.B.'s mother opted to split his vaccinations at this visit, so D.B. received his Hib and PCV7 vaccinations two weeks later, on January 7, 2009. *Id.* at 1080. At his six-month well child visit, D.B. received DTaP-IPV/HiB and Rotavirus vaccinations. *Id.* at 1079. Since his mother again opted to split his vaccinations, D.B. completed his six-month vaccinations two weeks later, on March 4, 2009, when he received the PCV7 and Hep B vaccinations (the latter being the vaccination at issue in this case). *Id.* at 1074.

[7] An ecchymosis is "a small hemorrhagic spot, larger than a petechia, in the skin or mucous membrane forming a non-elevated, rounded or irregular, blue or purplish patch." *Dorland's Illustrated Medical Dictionary* (32nd ed. 2012) [hereinafter "*Dorland's*"] at 1829. A petechia is "a pinpoint, non-raised, perfectly round, purplish red spot caused by intradermal or submucous hemorrhage." *Dorland's* at 1422. The pinna, also called an auricular, is "the portion of the external ear not contained within the head; the flap of the ear." *Dorland's* at 179.

[8] Epistaxis is "hemorrhage from the nose; also called nosebleed and nasal hemorrhage." *Dorland's* at 635.

Other hospital records noted that both parents were present. Those records provide different descriptions of D.B.'s history. For example, a March 15, 2009 coagulation disorder evaluation provides: "This lovely little boy was well until a few days ago, when he started to show bruises on his bottom, arms, and on his left lower lip. Had received a DTaP on March 3[9], and dad feels that his bruising began with this vaccination." Pet. Ex. 1 at 1068. A March 16, 2009 nursing admit note provides: "[D.B.] is an adorable 6 month old male who presented to his PCP with increased bruising over the past week. Received his 6 month immunization on 3/4/09 and since that time dad had noticed an increase in the amount of bruising on legs and back." *Id.* at 71. The discharge summary provides that D.B. presented with "1 week history of bruising, which parents feel has become more pronounced within the 3 days [prior to admission]." *Id.* at 729. This record also notes that D.B. lived with his mother but not his father. *Id.*

The attending physician was a pediatric hematologist, Dr. Eric Grabowski. Pet. Ex. 1 at 8. He ordered bloodwork, which was timestamped March 15, 2009 at 6:15 p.m. Pet. Ex. 1 at 559, 1069. This bloodwork found 5,000 platelets/µl (low, compared to a reference range of 150,000 – 400,000 platelets/µl), which was diagnosed as thrombocytopenia. Pet. Ex. 1 at 559, 1069. The same bloodwork found that hematocrit (red blood cells) constituted only 30.9% of whole blood, which was classified as mild normocytic anemia. *Id.* at 1069. A Coombs test was positive. *Id.* at 730. Based on the combined findings of thrombocytopenia, anemia, and the positive Coombs test, D.B. was diagnosed with Evans syndrome. *Id.*

D.B. was started on steroids, but his platelet count continued to drop despite the treatment. *Id.* at 730, 1069. D.B. was transitioned to a high-dose steroid, prednisone, and his platelet count increased initially to 23,000/µl by March 17, 2009, and then decreased slightly to 18,000/µl by March 18, 2009. *Id.* at 1059-61. A central venous line was placed for intravenous medication administration and continued blood draws, and D.B. was started on intravenous immunoglobulin ("IVIg") treatment, after which his platelet count increased to 60,000/µl**.** *Id.* at 730-31. His hematocrit level decreased. *Id.* By March 21, 2009, his platelet count increased further to 93,000/µl and his hematocrit was stable at 23.8 with "decreased evidence of hemolysis as evidenced by decreasing LDH and reticulocyte count." Thus, on March 21, D.B. was discharged home with oral steroids and instructions to follow up with Dr. Grabowski at the hematology clinic. *Id.* at 711-14.

On March 24, 2009, Dr. Grabowski saw D.B. for follow up. He recorded that labs from a prior day, before D.B. began IVIg, showed platelets at 158,000/µl, hemoglobin at 9.9, and hematocrit at 28.4. Pet. Ex. 1 at 1058. The same labs showed high serum IgG (at 1012 mg/dL), the significance of which was "discussed with Dr. Mark Pasternack; neither of us can attribute anything worrisome to it at the present time. Will repeat in 2-3 months." *Id.* The same labs showed normal IgA (18 mg/dL), IgM (52 mg/ dL), and serum protein pattern. *Id.*

[9] This medical record contains at least two errors: first, that D.B. received a DTaP vaccination where he actually received Hep B and Prevnar, and second, that the referenced vaccination(s) were on March 3, when they were actually on March 4. Pet. Ex. 1 at 1074.

By April 3, 2009, D.B.'s hematocrit had increased to 36 but his platelet count dropped to 30,000/µl**.** He was readmitted to Massachusetts General, where he received additional IVIg and was assessed with "Evans syndrome, stable hemolytic anemia but worsening thrombocytopenia." He was discharged the following morning. Pet. Ex. 1 at 714-15.

On April 10, 2009, D.B. returned to Massachusetts General with a several-day history of acute otitis media, vomiting, diarrhea, irritability, and increased bruising. His platelets had dropped below 5,000/µl**.** Pet. Ex. 1 at 683. D.B. underwent a normal CT scan to rule out intracranial bleeding and a normal ultrasound to rule out intussusception. *Id.* at 687-88. D.B.'s stool tested positive for rotavirus, and it was thought that the rotavirus was ramping up his immune system and exacerbating his Evans syndrome. *Id.* at 688. His platelet count remained below 5,000/µl for the first several days of his admission, and his hematocrit also dropped acutely. *Id.* D.B. received two platelet transfusions and one red blood cell transfusion. *Id.* He was started on 6-mercaptopurine, an immunosuppressant, in addition to his IVIg treatments. *Id.* D.B.'s overall clinical picture improved as his rotavirus improved, and he was discharged on April 17, 2009, with a platelet count of 9,000/µl, hemoglobin of 10.4, and a hematocrit of 30. *Id.* at 688, 695.

On April 26, 2009, D.B. returned to Massachusetts General for irritability. Pet. Ex. 1 at 682. He was well appearing on arrival and his exam and lab work was reassuring. *Id.* His inconsolability resolved and he was discharged that same day with instructions to follow up if his condition worsened. *Id.* On May 31, 2009, D.B. returned to Massachusetts General again due to increased bruising and fatigue while on a prednisone taper. *Id.* at 681. His exam was notable for mild bruising on his lower legs. *Id.* He had a platelet count of 40,000/µl and hematocrit of 31. *Id.* D.B was given prednisolone and discharged that same day with instructions to continue the steroid until he followed up with his hematologist, Dr. Grabowski. *Id.* On June 30, 2009, D.B. was readmitted for low platelet count, fatigue, irritability, and scattered petechiae. *Id.* at 675. He was given a high dose of Solumedrol and discharged home that same day. *Id.*

After blood drawn from his central venous line grew gram-positive cocci, on July 3, 2009, D.B. was again admitted to Massachusetts General, where he was administered steroids. On July 7, 2009, he was discharged home with instructions to continue the steroids. Pet. Ex. 1 at 50, 660.

On September 3, 2009, D.B. presented with irritability, abdominal pain, and fever. Pet. Ex. 1 at 642. Blood cultures turned positive "pretty rapidly" for gram negative rods. *Id.* On September 8, 2009, due to a large gallstone, his gallbladder was removed. *Id.* He was discharged on September 10, 2009. *Id.* From September 21 – October 2, 2009, D.B. was hospitalized again. He presented with persistent vomiting and diarrhea. *Id.* at 908. Despite new bruises appearing on his lower extremities, D.B.'s platelet cell count remained steady during his hospital course and he was discharged on his normal dosage of prednisone. *Id.* at 614.

Dr. Grabowski continued to monitor and manage D.B.'s care. He prescribed regular infusions through D.B.'s central venous line of pentamidine (an antimicrobial medication administered to people with poor immune function). Pet. Ex. 1 at 598. He also prescribed regular infusions of rituximab (an antibody targeting B cells), but that had the secondary effect of

hypogammaglobulinemia. *Id.* at 598, 767. At Dr. Grabowski's supervision, D.B. continued to undergo IVIg treatments. Pet. Ex. 2 at 82. In July 2010, D.B. underwent a bone marrow biopsy with the possibility of a transplant in mind. Pet. Ex. 1 at 777. His platelet levels remained steady and manageable until December 2010, when they dropped to 16,000/µl in association with an increase in bruising. Pet. Ex. 2 at 234. He was admitted overnight for observation and received a pentamidine infusion and IV solumedrol. Pet. Ex. 2 at 234.

In 2011, D.B. continued to suffer from gastrointestinal issues, bruising, bacterial infections, and chronic relapses. Pet. Ex. 2 at 138-230. In May 2012, D.B.'s mycophenolate and low-dose prednisone were discontinued, causing a significant increase in fresh bruises. Pet. Ex. 9 at 51. After his platelet count subsequently dropped to 20,000/µl, Dr. Grabowski and D.B.'s other physicians decided to start him on N-Plate.[10] *Id.* D.B.'s platelets stabilized over the next several months with his new regimen of N-Plate and IVIg. *Id.* at 58. D.B.'s bloodwork generally remained stable but he experienced intermittent relapses coupled with gastroenteritis. In December 2014, a repeat bone marrow biopsy yielded a diagnosis of bone marrow fibrosis, which was believed to be a side effect of his prolonged N-plate use. Pet. Ex. 17(b) at 69. As a result, Dr. Grabowski tapered down and then eliminated the N-plate. *Id.* By February 2015, D.B. was completely weaned off the N-plate but he developed frequent nose bleeds, severe abdominal pain, and gastrointestinal complications. He received frequent platelet transfusions. Pet. Ex. 17(a) at 182. In July 2015, another bone marrow biopsy showed favorable results and the N-plate was restarted. Pet. Ex. 17(a) at 130-31, 153-54.

Further medical records covering 2016 reflect that D.B.'s platelets and red blood cells are consistently low. In April 2016, he had normal IgG (719 mg/dL), low IgA (13 mg/dL), and low IgM (8 mg/dL). In May, June, and July 2016, IgG was low (at 530, 336, and 598 mg/dL, respectively) but it does not appear that IgA and IgM were tested. D.B.'s care remained supervised by pediatric hematologist Dr. Grabowski and D.B.'s diagnosis has remained Evans syndrome with associated hypogammaglobulinemia. *See generally* Pet. Ex. 26.

3. Testimony of Petitioner Tia Bucci (D.B.'s Mother)

D.B.'s mother offered fact testimony at the entitlement hearing in November 2016. Tr. 6-54, 135-39. Since approximately 2006, she has been employed as a licensed radiologic technologist at Massachusetts General Hospital. *Id.* at 7. D.B. is her first and only child. *Id.* at 6. The mother testified that when D.B. was born, she was married to and living with his father, petitioner Nicholas Bucci. Tr. 7. When D.B. was approximately two weeks old, his father left

[10] The U.S. Food and Drug Administration (FDA) initially approved use of N-plate (romiplostim) to treat "low blood platelet counts in *adults* with chronic (idiopathic) immune idiopathic thrombocytopenia (ITP) when certain other medicines, or surgery to remove the spleen have not worked well enough." *See* FDA, *Postmarket Drug Safety Information for Patients and Providers – N-Plate (romiplostim) information*, available at https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm280200 htm (last accessed March 12, 2019). Petitioner Ms. Tia Bucci testified that in 2011, D.B. was "the first pediatric patient to be accepted" by the FDA to receive N-plate. Tr. 39. Seven years later, the FDA officially and broadly approved use of N-plate in pediatric patients 1 year of age and older with ITP for at least 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. *See* FDA, *N-Plate Supplement* 163 (dated December 14, 2018), available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process.

the home and did not see D.B. unless the mother was there. *Id.* at 7, 15-16. The mother recalled that D.B. was generally a normal and healthy child for the first six months of life until he received the hep B vaccination at issue on March 4, 2009. *Id.* at 8-9. That evening, D.B. was fussy, crying and irritable. *Id.* at 9-10. He was also constantly sticking his fingers in his ear and pulling and tugging on his ear. *Id.* at 10. The mother thought he had an ear infection. *Id.*

These issues persisted for several days until March 7, 2009, when the mother called the pediatric practice and brought D.B. in for an appointment. *Id.* The mother recalled that at this time, D.B. had a "very small, round, black and blue" mark "exactly at the injection site of the Hep B vaccination." *Id. at* 11. Additionally, D.B. had a "pink mark on the ear" which "looked like his skin had just been irritated from him consistently sticking his finger in his ear and pulling at his ear." *Id.* The mother did not recall the pediatrician raising any concerns about these findings. *Id.* She believed that D.B.'s fussiness, mark at the injection site, and mark on the ear all resolved within one to two days after the March 7, 2009 pediatrics appointment. *Id.* at 11-12.

The mother recalled that on March 12, 2009, she had her first appearance in divorce court, which represented "the beginning of the end of her marriage." Tr. 17. Upon returning home, she observed a purple bruise on D.B.'s right lower ankle. *Id.* She initially didn't think much of it because D.B. was just beginning to move around, crawl, and roll over. *Id.* at 18. On March 13, she observed a couple more bruises on his shins. *Id.* On March 14, the bruising had spread to his thighs, abdomen, and the upper extremity portion. *Id.* at 19. She called the pediatric practice and spoke to a nurse practitioner who suggested that it was vascular and to keep D.B. warm and observe him further. *Id.*

On March 15, 2009, upon waking up and attending to D.B., the mother observed that the bruising had multiplied. She stated that the prior bruise at the vaccine administration site observed on March 7 was significantly different from the bruises which began approximately one week later. The latter were more significant in color, size, and depth. Tr. 14, 25-26.

Also on March 15, 2009, there were new "tiny red dots" resembling what could be marked with a ballpoint pen, "all over his face down to his ankles." *Id.* at 12-13, 19. She stated that this was the first time she saw these dots, which were later referred to as petechiae. *Id.* They were significantly different from the findings on D.B.'s ear observed back on March 7, 2009. Tr. 13.

The mother called and informed D.B.'s father that there might be something really wrong with their child. *Id.* at 20-21. The mother brought D.B. to the pediatric clinic and was then referred to Massachusetts General Hospital, where she was joined by the father, who had not been living with or seeing D.B. regularly or without his mother for several months. *Id.* at 21-23. Additionally, the mother did not have time at the hospital to share any details about D.B.'s post-vaccination course with the father. *Id.* at 21-23. Thus, any history obtained from the father would be inaccurate. *See, e.g., id.* at 31, 50-51. However, the father did remain at the hospital and became more involved in D.B.'s life afterwards. *See, e.g., id.* at 30, 32, 47.

The mother testified, consistent with the medical records summarized above, that D.B.'s diagnosis remains Evans syndrome. *Id.* at 38. He has received and continues to receive various treatment for that condition. *Id.* His blood counts dictate his physical activity level. *Id.* If his platelets fall below 40,000/µl, his physical activity must be restricted, for example, he cannot go out for recess, play on the jungle gym, or participate in physical sports. *Id.* at 38-39.

II. LEGAL STANDARD[11]

The Vaccine Act was established to compensate vaccine-related injuries and deaths. Section 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Rooks v. Sec'y of Health & Human Servs.,* 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, *reprinted in* 1986 U.S.C.C.A.N. at 6287, 6344).

A petitioner must prove that he or she is entitled to compensation under the Vaccine Program. A petitioner's burden of proof is by a preponderance of the evidence. § 300aa-13(a)(1). A petitioner may demonstrate entitlement in one of two ways. The first is to demonstrate a "Table injury," that is, a specified injury within a specified period of time following administration of a vaccine listed on the Vaccine Injury Table. § 300aa-14(a). In the present case, petitioners do not allege a Table injury, nor would the record support such an assertion.

Therefore, petitioners must demonstrate that the vaccine was the cause-in-fact of the vaccinee's injury. In order to prevail in an "off-Table Injury," claim, a petitioner must meet the three prong test provided by the *Althen* court: "(1) a medical theory casually connecting the vaccine and injury; (2) a logical sequence of cause and effect showing the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between the vaccine and the injury. *Althen v. Sec'y of Health & Human Servs.,* 418 F.3d 1274, 1278 (Fed. Cir. 2005).

The legal standard is by a preponderance of the evidence." §300aa-13(a)(1)(a). This does not require "conclusive scientific evidence" or "certainty." *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1322 (Fed. Cir. 2010). Instead, the standard has been interpreted to mean that a fact is more likely than not. *Id.* at 1322 n.2. The Federal Circuit has observed that this preponderance standard enables "the finding of causation in a field bereft of complete and direct proof of how the vaccines affect the human body." *Althen*, 418 F.3d at 1280. Petitioners must establish each *Althen* prong by the preponderance of the evidence. *Caves v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 119, 132 (2011), *aff. per curiam*, 463 Fed. Appx. 932 (Fed. Cir. 2012).

[11] Decisions of special masters (some of which I cite in this decision) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). Decisions from the Court of Federal Claims are only binding in the same case on remand. *Id.* Federal Circuit decisions concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd*, 104 Fed. App'x 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504278, at *7 n. 12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. See *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir.1991). Thus, petitioners must provide a reputable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994). Petitioners must establish each *Althen* prong by the preponderance of the evidence. *Caves v. Sec'y of Health & Human Servs.,* 100 Fed. Cl. 119, 132 (2011), *aff. per curiam*, 463 Fed. Appx. 932 (Fed. Cir. 2012).

Petitioners cannot establish entitlement to compensation based solely on their assertions. Rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 300aa-13(a)(1). In determining whether petitioners are entitled to compensation, the special master shall consider all material contained in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 300aa-13(b)(1)(A). The undersigned must weigh the submitted evidence and the testimony of the parties' offered experts and rule in petitioners' favor when the evidence weighs in their favor. *See Moberly*, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence"); *Althen*, 418 F.3d at 1280 ("close calls" are resolved in petitioner's favor).

Causation is determined on a case by case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention so long as the petitioner supplies the medical opinion of an expert. *Id.* at 1279–80. The court also indicated that, in finding causation, the fact-finder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Id.* at 1280.

Once a petitioner fulfills the *Althen* test, the burden of persuasion shifts to respondent to show that the alleged injury was caused by a factor unrelated to the vaccination. *Knudsen*, 35 F.3d 543 at 548; § 13(a)(1)(B). Respondent has the burden of demonstrating that "a factor unrelated to the vaccination is the more likely or principal cause of the injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury." *Deribeaux v. Sec'y of Health & Human Servs.,* 717 F.3d 1363, 1369 (Fed. Cir. 2013). Section 13(a)(2) specifies that factors unrelated "[do]not include any idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor, injury, illness, or condition."

Regardless of whether the burden ever shifts to respondent, the special master may consider the evidence presented by respondent in determining whether the petitioner has established a prima facie case. *Flores v. Sec'y of Health & Human Servs.,* 115 Fed. Cl. 157, 163 (2014) (citing *Stone v. Sec'y of Health & Human Servs.,* 676 F.3d 1373, 1379 (Fed.Cir.2012) ("[E]vidence of other possible sources of injury can be relevant not only to the 'factors

unrelated' defense, but also to whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question.")).

In Vaccine Act cases, expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo*, 617 F.3d at 1339 (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95). In Vaccine Program cases, these factors are used in the weighing of the scientific evidence actually proffered and heard. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66–67 (Fed. Cl. 2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"), *aff'd*, 420 F. App'x 923 (Fed. Cir. 2011). The flexible use of the *Daubert* factors to determine the persuasiveness and/or reliability of expert testimony in Vaccine Program cases has routinely been upheld. *See, e.g., Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 742–45 (2009).

Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1362 (Fed. Cir. 2000)). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280; *Knudsen*, 35 F.3d at 551 ("If the evidence (on alternative cause) is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded").

III. EXPERT TESTIMONY

A. Petitioners' Expert, Dr. Edwin Forman

1. Dr. Forman's Qualifications

Petitioners submitted one report and hearing testimony from Dr. Forman. Pet. Ex. 14; Tr. 55-135. He obtained a bachelor's degree from Brown University in 1956 and a medical degree from the University of Pennsylvania in 1960. Pet. Ex. 15 at 3. Afterward, he practiced general pediatrics in the United States Air Force for three years, then completed an internship and residency in Pediatrics at Johns Hopkins Hospital, and a two-year fellowship in Pediatric Hematology and Oncology at the United States Public Health Service in Chicago, Illinois. *Id.*; Tr. 57. For approximately four decades, he practiced those specialties at Rhode Island Hospital and taught them at Brown University, where he rose to the rank of full professor. Pet. Ex. 15 at 3. Brown University has established a chair in honor and recognition of Dr. Forman's work with children with blood disorders and cancers, as well as his work in biomedical ethics. Tr. 59.

Since 2009, Dr. Forman has been affiliated with Mount Sinai School of Medicine in New York, where he is an attending physician and a full Professor of Pediatrics. He is board-certified in pediatrics and pediatric hematology-oncology. He was elected as a member of the American Pediatric Society and to the American Board of Pediatrics Committee on Hematology-Oncology, which writes the certifying exam. Pet. Ex. 15 at 1-7; Tr. 57-59.

Dr. Forman estimated that he has worked with more than 150 patients with ITP and approximately seven patients with Evans syndrome, most of whom he diagnosed himself. Tr. 60. As part of his regular practice, he endeavors to keep up with the literature published on autoimmune diseases, and their suspected triggers, diagnosis, and treatment. Tr. 60. He has both provided opinions and testified in a few prior cases in the Vaccine Program. Tr. 62.

I admitted Dr. Forman as an expert in pediatric hematology and oncology, particularly as those areas relate to evaluation, diagnosis, and treatment of autoimmune diseases including Evans syndrome and ITP. Tr. 62-63.

2. Dr. Forman's Opinion Regarding Evans syndrome

Dr. Forman and the three other experts in this case all agreed that D.B.'s prevailing diagnosis is Evans syndrome. Pet. Ex. 14 at 1; Tr. 64. Dr. Forman defined Evans syndrome as autoimmune hematologic cytopenias (a reduction in the number of mature blood cells caused by antibodies that destroy them) in at least two lines after exclusion of any known etiology. Neutrophils are occasionally involved. However, the most common presentation as in D.B.'s case, is that the two cell lines affected are platelets and red blood cells. Evans syndrome has two diagnostic requirements: (1) bloodwork confirming two low blood cell counts and (2) a Coombs- or direct-antibody test which shows that the patient's gammaglobulin is binding to the red blood cells, which confirms that the reduction in red blood cells is due to an autoimmune process. However, Evans syndrome remains a diagnosis of exclusion of other autoimmune conditions. *See* Pet. Ex. 14 at 1; Tr. 65-66, 69.[12]

[12] *See also Dorland's* at 1922.

The reduction in red blood cells is referred to as hemolytic anemia. Pet. Ex. 14 at 1; Tr. 65-66.[13] Dr. Forman generally did not discuss its consequences.

The reduction in platelets is referred to as thrombocytopenia. This results in blood leaking from numerous vessels close to one another, manifesting as spontaneous bruising without trauma. This condition is referred to as immunologic thrombocytopenia purpura (ITP)). Pet. Ex. 14 at 1; Tr. 65-66.[14] Dr. Forman acknowledged that ITP can occur on its own (without involvement of a second cell line). ITP generally has an acute onset, is benign, and resolves on its own without treatment. Ninety percent of cases resolve within a year. Tr. 66. Dr. Forman opined that in contrast to acute ITP, Evans syndrome is chronic and almost never spontaneously remits. Evans syndrome is associated with increased morbidity and mortality. It has a "totally different course and different management." Tr. 66-67.

Dr. Forman opined that for both ITP and Evans syndrome, the first-line treatment is intravenous gammaglobulin (IVIg), which "chemically paralyzes" the spleen, which normally slows down circulation and enables phagocytes to pick off platelets and red cells coated with gammaglobulin. Tr. 94. Through this mechanism, IVIg raises the cell count 70-80% of the time. Tr. 94. It is less successful – perhaps 60% - in Evans syndrome. Tr. 94, 122-23. Dr. Forman noted that other treatments include removing the spleen, which is less desirable because it makes the patient more susceptible to infection, and N-plate which stimulates megacaryocytes, the immature cells that turn into platelets. Tr. 95-96.

Dr. Forman agreed that Evans syndrome is a rare diagnosis, but he referenced a study authored by Aladjidi et al.[15] on all patients under 18 years old living in France and diagnosed or followed up with autoimmune hemolytic anemia. There were 265 such patients. Detailed data from each patient's medical records was checked. Ninety-nine (37%) of the patients with autoimmune hemolytic anemia *also* had ITP, which converted their diagnosis to Evans syndrome. Pet. Ex. 21(f) at 2.

At the hearing, Dr. Forman (as well as counsel and the other experts) inadvertently misstated that the Aladjidi article was of 265 patients diagnosed originally with *ITP*, of which 37% were also found to have *hemolytic anemia* leading to the diagnosis of Evans syndrome. Tr. 68-69. *Id.* at 1. This is significant because Dr. Forman went on to say that there are an "incredible number" of patients with pediatric ITP. If ITP is "incredibl[y]" common and a greater-than-expected number of patients with ITP also have hemolytic anemia and by extension Evans syndrome, then Evans syndrome is more common than is currently recognized by the medical community. Tr. 69. However, compared to ITP, there are fewer cases of hemolytic anemia. Aladjidi's finding that 37% of 265 patients with hemolytic anemia also have ITP and by

[13] *See also Dorland's* at 79.

[14] *See also Dorland's* at 1829.

[15] N. Aladjidi et al., *New Insights Into Childhood Autoimmune Hemolytic Anemia: A French National Observational Study of 265 Children*, 96 Haematologica 655 (2011) [Pet. Ex. 21(f)].

extension Evans syndrome suggests that Evans syndrome is more common than reported by other articles – but not as common as Dr. Forman projects.

Dr. Forman opined that in common variable deficiency syndrome (CVID), the word to be emphasized was "*variable*." He described CVID as "an immune deficiency state or immune dysfunction state . . . associated with a deficiency of immunoglobulins." Tr. 87. There are three important immunoglobulins involved here. IgG attacks germs and a low level of IgG is associated with a significantly increased susceptibility to infection." Tr. 87. IgA and IgM are also involved. Tr. 87. At least two of these gammaglobulins must be low for a diagnosis of CVID to be made. Tr. 87. Other immune deficiencies and other cases must be ruled out. Tr. 87. Dr. Forman opined that CVID most often presents in the second or third decade of life and perhaps only 10% of cases present in children. Pet. Ex. 14 at 3; Tr. 87. Dr. Forman stated that there are "several different kinds" of CVID." Tr. 88. However, he also said that CVID has "a whole different course and different things to look for, like pulmonary involvement and early treatment before it becomes lethal." Tr. 88. Dr. Forman opined that IVIg, rituximab, and immunosuppressants can prevent an accurate reading of a patient's gammaglobulins, thus preventing an accurate diagnosis of CVID. Pet. Ex. 14 at 3[16]; Tr. 88-90, 121. Additionally, "[a] diagnosis of CVID before the age of six years is particularly problematic because of the immunologic immaturity and the persistence of hypogammaglobulinemia of infancy in some children." Pet. Ex. 14 at 3.[17] "Most children present with a history of recurrent and significant infections." Pet. Ex. 14 at 3.

Dr. Forman first opined that "[CVID] usually doesn't present this way, but it can evolve into Evans Syndrome." Tr. 88. Later in the testimony, when I asked for confirmation of this course, Dr. Forman stated that usually, patients are diagnosed first with CVID "because pulmonary symptoms are the first projection, and as they are followed, they can develop autoimmunity against platelets, red cells, and even the neutrophils [culminating in a diagnosis of Evans syndrome]. Now, can it happen the other way around? Can Evans be the first sign of CVID? I don't know. It's possible." Tr. 101-02.

Dr. Forman opined: "To presume that [D.B.] had an underlying condition that caused his Evans syndrome would not be correct. Everyone carries some genetic mutations/variations, but it takes a precipitant to bring the disease on. Thus, the precipitant is the cause of the clinical situation." Pet. Ex. 14 at 2. In other words, a precipitant or trigger needs to begin the autoimmune process against the blood cells in Evans syndrome. At the entitlement hearing, Dr. Forman offered the analogy that certain people have a genetic predisposition to develop lung cancer, but they need a trigger, such as smoking, to initiate that process. (People who do not have the genetic predisposition, but do smoke, are unlikely to develop lung cancer.) Both the genetic predisposition and the trigger are necessary for the condition to develop. Tr. 71, 117.

[16] Citing Vaccine Injury Table, 42 C.F.R. § 100.3(a).

[17] Citing M. Hogan & N. Wilson, *Common Variable Immunodeficiency in Children*, Wolters Kluwer Health – UpToDate May 27, 2014 [Pet. Ex. 20(h); P. Ogershok et al., *Spectrum of Illness in Pediatric Common Variable Immunodeficiency*, 97 Ann. Allergy Asthma Immunol. 653 (2006) [Pet. Ex. 20(i)].

3. Dr. Forman's Opinion Regarding Causation between Hepatitis B Vaccine and Evans syndrome

Dr. Forman largely left the theory of causation to be addressed by Dr. Byers, the immunologist retained by petitioners. However, he opined that in a small number of individuals with an underlying vulnerability, "the measles vaccine can lead to ITP." Pet. Ex. 14 at 2.[18] He opined that there were also numerous reports linking hepatitis B vaccine and hepatitis B infections to Evans syndrome. Pet. Ex. 14 at 3.[19] "Note: the antigens in the hepatitis B vaccine are derived from the hepatitis B virus." Pet. Ex. 14 at 3. On cross-examination, Dr. Forman referenced one case report on hepatitis B vaccine and Evans syndrome in a 33-year-old man. However, petitioners' counsel objected to that line of questioning on the grounds that Dr. Forman was not presented to discuss the medical literature on causation by hepatitis B. Accordingly, Dr. Forman's testimony on this subject was limited. Tr. 103-07. He also opined that hepatitis B vaccine is one of many possible triggers for Evans syndrome. Tr. 112-14.

4. Dr. Forman's Opinion Regarding Sequence of Cause and Effect

As discussed below, respondent's expert Dr. Gans opined that she believed it was likely that D.B.'s Evans syndrome was the first manifestation of what is actually CVID. Dr. Forman largely disagreed. D.B.'s treating hematologist, Dr. Grabowski, observed that at the beginning of his disease course, before IVIg was started, D.B.'s IgG was somewhat high and his IgM and IgA were within normal limits, meaning that he could not be diagnosed with CVID. Tr. 88-92 (discussing Pet. Ex. 1 at 1058). Once D.B. was started on IVIg (on which he has remained for years), subsequent tests of the gammaglobulins did not accurately represent what was produced by D.B.'s own body and what was being delivered via IVIg. Dr. Forman also explained that accurate gammaglobulin levels cannot be obtained until IVIg has been withdrawn for several months. Dr. Forman acknowledged that Dr. Grabowski may have been "entertaining" that diagnosis, which does have a late onset and might "possibly" start with the development of

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[18] Citing American Academy of Pediatrics, *Red Book: Report of the Committee on Infectious Diseases* (30th ed. 2009) at 544 [Pet. Ex. 20(a)]; V. Vlacha et al., *Recurrent Thrombocytopenic Purpura After Repeated Measles-Mumps-Rubella Vaccination*, 97 Pediatrics 738 (1996) [Pet. Ex. 20(b)]; C. Black et al., *MMR Vaccine and Idiopathic Thrombocytopaenic Purpura*, 55 Br. J. Clin. Pharmacol. 107 (2002) [Pet. Ex. 21(c)]; E. Miller et al., *Idiopathic Thrombocytopaenic Purpura and MMR Vaccine*, 84 Arch. Dis. Child 227 (2001) [Pet. Ex. 20(d)].

[19] Citing P. Poullin & B. Gabriel, *Case Report: Thrombocytopaenic Purpura After Recombinant Hepatitis B Vaccine*, 344 Lancet 1293 (1994) [Pet. Ex. 20(j)]; P. Finielz et al., *Systemic Lupus Erythematosus and Thrombocytopaenic Purpura in Two Members of the Same Family Following Hepatitis B Vaccine*, 13 Nephrol. Dial. Transplant 2421 (1998) [Pet. Ex. 20(k)]; E. Martinez & P. Domingo, *Case Report: Evans syndrome Triggered by Recombinant Hepatitis B Vaccine*, 15 Clinical Infectious Diseases 1051 (1992) [Resp. Ex. P]; F. Ronchi et al., *Thrombocytopaenic Purpura as Adverse Reaction to Recombinant Hepatitis B Vaccine*, 78 Arch. Dis. Child 273 (1998) [Pet. Ex. 20(m)]; H. Nuevo et al., *Thrombocytopaenic Purpura After Hepatitis B Vaccine: Case Report and Review of the Literature*, 23 Ped. Infect. Disease J. 183 (2004) [Pet. Ex. 20(n)]; A. Polat et al., *Severe Thrombocytopenia after Hepatitis B Vaccine in an Infant from Turkey*, 26 Vaccine 6495 (2008) [Pet. Ex. 20(o)]; D. Neau et al., *Immune Thrombocytopenic Purpura after Recombinant Hepatitis B Vaccine: Retrospective Study of Seven Cases*, 30 Scand. J. Infect. Dis. 115-18 (1998) [Pet. Ex. 20(p)]; R. Maezono & A. Escobar, *Thrombocytopenic Purpura after Hepatitis B Vaccine*, 76 J. Pediatr. (Rio J.) 395 (2000) [Pet. Ex. 20(q)]; K. Sakha et al., *Hepatitis B Vaccine and Infantile Idiopathic Thrombocytopaenic Purpura*, 15 Med. J. of Islamic World Acad. Sci. 149 (2005) [Pet. Ex. 20(r)]; A. Kalayci et al., *Case Report: Evans syndrome Related to Hepatitis B Virus Infection: A Case that Responded to Lamivudine Therapy*, 32 J. Ped. Gastro. & Nutrition 493 (2001) [Pet. Ex. 25].

Evans syndrome. Dr. Grabowski and the other treating physicians have never diagnosed or treated D.B. for CVID. Tr. 98-102, 96-110.

In his report, Dr. Forman stated that it would be incorrect to presume that D.B. had an underlying genetic condition that caused his Evans syndrome. Pet. Ex. 14 at 2. There is no specific verifiable genetic vulnerability associated with Evans syndrome and none was found in D.B.

Dr. Forman noted that the hepatitis B vaccine's reported possible side effects include irritability, which is often associated with children pulling their ears, as well as earache. In this case, D.B.'s mother reported a history of "ear pulling" and he was recorded to have a "red mark" on the ear. Thus, it was more likely that the ear was irritated by D.B. himself and less likely that this was a bruise representing an early sign of an autoimmune disease like ITP or Evans syndrome. There was also no indication of an ear infection. Pet. Ex. 14 at 2; Tr. 78-82.

Dr. Forman testified that D.B.'s "dime-sized bruise with induration on the right thigh" where the hepatitis B vaccination was administered was a typical vaccine reaction. He did not believe this was unusual or suggestive of either ITP or Evans syndrome. Tr. 78-79. As discussed below, respondent's experts, Dr. Gans and Dr. Gill, attributed more significance to this bruise, but it seemed that Dr. Forman had more experience in vaccinating a wide array of children both with and without bleeding disorders and that his testimony about the common occurrence of transient bruising after vaccination was more credible.

Dr. Forman also opined that D.B.'s fussiness, mark on the ear, and mark at the injection site resolving within a few days was consistent with his understanding of benign post-vaccination reactions. Tr. 82.

Dr. Forman opined that "acute ITP almost always begins with diffuse petechiae and/ or purpura and/ or bleeding and not in a single spot." Pet. Ex. 14 at 2.[20] "The multiple bruises and diffuse petechiae, with or without bleeding, are generally shocking enough for parents to bring their child in for medical care within a day, as was the case here." *Id.* at 2-3.

Dr. Forman opined that "in a minority of patients, there's immunodysfunction in the patient and in relatives." Tr. 71. Dr. Forman opined that in this case, if respondent's experts were correct that D.B.'s mother had ulcerative colitis and endometriosis, that could be suggestive that D.B. had inherited immunodysfunction. Tr. 70-71.[21]

Dr. Forman maintained that even if there were some evidence of immune dysfunction in D.B. and/ or his mother, a trigger for the development of Evans syndrome would still be needed and that the hepatitis B vaccine was the trigger in this case. Pet. Ex. 14 at 2; Tr. 71.

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[20] Citing *Nelson Textbook of Pediatrics* (18th ed. 2007) at 2082 [Pet. Ex. 20(e)]; *Nathan and Oski's Hematology of Infants and Childhood* (7th ed. 2007) at 1558-59 [Pet. Ex. 20(f)].

[21] The mother insisted that the mention of ulcerative colitis in her medical record was in error. Respondent contended that the mother's diagnosed endometriosis is also an autoimmune condition. Petitioners disputed same and the literature was equivocal. As her condition would provide at most a clue I elected not to do a collateral analysis of the mother's diagnoses or their significance.

5. Dr. Forman's Opinion Regarding Timing

As noted above, Dr. Forman did not believe that D.B.'s post-vaccination irritability, mark on the ear, and mark at the vaccination site represented the first manifestations of Evans syndrome. Rather, Dr. Forman accepted the mother's testimony that D.B.'s petechiae and bruising began approximately eight days after the vaccination, on March 12, 2009. Dr. Forman noted that these symptoms were consistent with Evans syndrome and that when they first manifest, they are quite alarming to both parents and treating physicians. That occurred in this case: the mother promptly called and then brought D.B. in to the pediatric practice, and the physician ordered bloodwork. Tr. 73.

Dr. Forman opined that this temporal relationship was appropriate. Pet. Ex. 14 at 2. He opined that from the moment antibodies are formed, the platelet count drops within twenty-four hours. In many cases of Evans syndrome, a trigger is not identified. However, if a trigger for Evans syndrome is identified, the time from the platelet count dropping to when the condition is visibly apparent, e.g., bruising, is usually one to six weeks. This is a bell-shaped curve. The peak is around 10-14 days.

For the aforementioned reasons, Dr. Forman opined that the hepatitis B vaccine D.B. received on March 4, 2009, more likely than not caused the onset of his Evans syndrome with onset approximately eight days afterwards. Pet. Ex. 14 at 2-4[22]; Tr. 74-80, 85-86.

B. Petitioners' Expert, Dr. Vera Byers

1. Dr. Byers's Qualifications

Petitioners presented three expert reports and testimony from Dr. Byers. Pet. Exs, 7, 16; Tr. 139-204; Pet. Ex. 27 (submitted post-hearing). She obtained a bachelor's degree in microbiology in 1965, a M.A. in microbiology in 1967, and a Ph.D. in immunology in 1969, all from the University of California – Los Angeles. Pet. Ex. 8 at 1. She completed a fellowship in protein chemistry at Abbott Laboratories from 1969-1971. Afterward, she completed a fellowship in clinical immunology from 1971-1973, obtained an M.D. in 1981, then completed a three-year residency in internal medicine from 1981-1984, all from the University of California - San Francisco (UCSF). *Id.*

From 1988-1994, she was the director of the Positive Action Health Care HIV Clinic in California. Pet. Ex. 8 at 3-4; Tr. 142-43. Dr. Byers testified that during her medical education and her work at the HIV clinic, she did see patients with thrombocytopenia. Tr. 142-43. She has treated approximately 30 children and adults diagnosed with CVID. Tr. 184. She has never treated any children or adults with Evans syndrome. Tr. 184. She stated that she practiced medicine for about twenty years, but she has not done so since at least 2006. Tr. 183.

Dr. Byers has devoted a significant portion of her career to consulting with several biotech companies, some involved with developing vaccines. Pet. Ex. 8 at 2-4; Tr. 141-42. Dr. Byers is currently medical director and a consulting medical toxicologist for pharmaceutical

[22] Citing Vaccine Injury Table, 42 C.F.R. § 100.3(a).

companies at Immunology Inc. Pet. Ex. 8 at 2. She has been board-certified in internal medicine since 1984, but she has never been board-certified in immunology. *Id.*; Tr. 139.

She has frequently served as an expert witness in civil litigation and in the Vaccine Program, where she has previously been qualified as an expert in immunology. In this case, petitioners proffered and I accepted Dr. Byers as an expert in the area of clinical immunology, particularly as it relates to evaluating and determining whether particular vaccines can trigger autoimmune diseases, including ITP and Evans syndrome.[23]

2. Dr. Byers's Opinion Regarding Evans syndrome

Over the litigation of this case, Dr. Byers offered various explanations of the medical conditions involved, of which she had limited treating or research experience. In her first report, Dr. Byers suggested that D.B. had CVID which is an autoimmune disorder with many possible manifestations, including ITP and Coombs-positive hemolytic anemia. Pet. Ex. 7 at 2-3. She also said that "Evan[s] syndrome is really ITP, with a Coombs-positive anemia attached." *Id.* at 5. Respondent's expert Dr. Gans then raised the argument that ITP has different pathophysiology and etiology; thus, its findings cannot be extrapolated to Evans syndrome. Resp. Ex. D at 2-3 (discussed further below). Dr. Byers answered that this "doesn't make much difference." Pet. Ex. 16 at 3. Dr. Byers stated that "most authors classify Evans syndrome as a secondary form of ITP, along with ALPS, anti-phospholipid syndrome, and SLE, as [Dr. Byers] did [in her first report]." *Id.* She opined that ITP and Evans syndrome are each very rare. They are more difficult to compare because each study uses the "assay du jour" rather than the same methods used in previous studies, which would help to evaluate the data as a whole. *Id.*[24] Dr. Byers opined that ITP and Evans syndrome each involves a "seriously dysregulated" immune system. *Id.* Each condition is "very heterogeneous." *Id.*[25] "This heterogeneity carries through all the papers and reviews attempting to characterize either of the syndromes and provide very unconvincing evidence for either a difference or a characteristic profile for either disease." *Id.* Dr. Byers is not persuaded by Dr. Gans's other distinctions between ITP and Evans. *Id.*[26] For

[23] In his post-hearing brief, respondent contends that Dr. Byers overstated or misrepresented certain qualifications. Resp. Post-Hearing Brief at 16-17, citing Pet. Ex. 8. Respondent also criticizes Dr. Byers's reliability. Respondent cites to multiple past opinions by special masters finding Dr. Byers's opinions to be confusing, speculative, or unsupported. Resp. Post-Hearing Brief at 16-17. I take these points and will not comment on them, except to state that in this case, I found Dr. Byers's first two reports and her hearing testimony to be confusing. I directed her (as well as Dr. Gans) to file an additional report. These were helpful in answering some of the specific questions I raised. Had these issues been appropriately addressed before the hearing, I – and counsel - would have had the opportunity to ask appropriate questions rising from those reports.

[24] Citing W. Wang et al., *Immunoregulatory Abnormalities in Evans Syndrome*, 15 Am. J. Hematol. 381 (1983) [Resp. Ex. I]; S. Savasan et al., *Increased Lymphocyte Fas Expression and High Incidence of Common Variable Immunodeficiency Disorder in Childhood Evans Syndrome*, 125 Clin. Immun. 224 (2007) [Resp. Ex. J]; D. Teachey et al., *Unmasking Evans Syndrome: T-cell Phenotype and Apoptotic Response Reveal Autoimmune Lymphoproliferative Syndrome (ALPS)*, 15 Blood 2443 (2005) [Resp. Ex. K].

[25] Citing S. Savasan (2007) [Resp. Ex. J].

[26] Citing D. Cines & V. Blanchette, *Medical Progress: Immune Thrombocytopenic Purpura*, 346 N. Eng. J. Med. 995 (2002) [Pet. Ex. 21(a)].

various reasons, which are in truth difficult to summarize, Dr. Byers opined that "the information differentiating Evans from ITP is not convincing, and the appropriate name for the syndrome is ITP-Evans." *Id.*

At the hearing, Dr. Byers repeated the inadvertent characterization that Aladjidi et al.[27] found that out of 265 pediatric patients diagnosed with *ITP*, 37% were also found to have hemolytic anemia thereby converting their diagnosis to Evans syndrome. Tr. 169-70. From this study, Dr. Byers extrapolated that the Vaccine Adverse Events Reporting System (VAERS) included approximately 200 reports of hepatitis B vaccine and ITP, but "a substantial portion of those" probably have Evans syndrome. Tr. 170. However, as discussed above in the summary of Dr. Forman's testimony, those patients' original diagnosis was *hemolytic anemia* (the less common condition) and were found to also have ITP. This undercuts both of petitioners' experts' opinions that Evans syndrome is more common than is currently recognized.

After the hearing, I directed Dr. Byers to submit a supplemental expert report clarifying her opinions on Evans syndrome and the other issues in this case. At one point, she opined: "Evans syndrome is usually thought to be a *peripheral* disease, in other words it's not a lack of the ability of the bone marrow to produce the immature precursor cells, but rather the antibodies that erroneously bind to the *mature circulating cells.*" Pet. Ex. 27 at 4 (emphasis added).

However, further down on the same page, Dr. Byers seems to contradict herself by stating that Evans syndrome and other chronic blood disorders do not just involve an attack on the mature circulating cells in the periphery, but also involve an attack on the immature precursor cells:

> The underlying pathology of acute ITP, which is one component of Evans syndrome is acknowledged to be antibodies directed against mature platelets which tag them as targets to be removed by the spleen. The other component is also antibody-mediated, but the antibodies are now directed against red blood cells. The two components can present together as happened here or occur following one or the other. *The question here is what causes chronic ITP or hemolytic anemia*. Several reviews feel the difference is that acute ITP or hemolytic anemia is due only to antibodies removing the mature cells from the peripheral circulation, but *chronic disease is also associated with both immune-mediated platelet destruction and destruction of the platelet precursors called megacaryocytes by cytotoxic T lymphocytes. In other words, there is both activation of auto-reactive T and B cells, and attack on both the mature cells and their precursors."*

Pet. Ex. 27 at 4 (emphasis added).

[27] Aladjidi et al. (2011) [Pet. Ex. 21(f)].

In support of this formulation of *chronic* ITP, Dr. Byers submitted two articles by Robert McMillan and colleagues.[28] McMillan observes that many patients with chronic ITP produce antibodies against more than one glycoprotein, which has been "attributed to epitope spreading." Pet. Ex. 28(j) at 4 (not elaborating on the concept of epitope spreading). The 2007 review and a 2009 follow-up review both report that chronic ITP patients not only have decreased platelets, but also morphological damage to the megacaryocytes. Pet. Ex. 28(j); Pet. Ex. 28(m). These articles provide some support for a distinction between the physiology of acute and chronic ITP, with chronic ITP bearing more similarity to Evans syndrome, possibly rooted in immune attack on the magacaryocytes. Respondent's expert Dr. Gans did not respond specifically to these articles but acknowledged during the hearing that chronic ITP had more similarity to Evans syndrome and may share some of the same pathways. Tr. 268-69.

While Dr. Byers's contradictory statements regarding the pathophysiology of Evans syndrome and chronic ITP may reflect some of the uncertainty in the medical community about these conditions, her statements also reflect a lack of commitment or understanding of her own causation opinion, which is not helpful to petitioners' case.

3. Dr. Byers's Opinion Regarding Causation between Hepatitis B Vaccine and Evans syndrome

Dr. Byers initially pointed to molecular mimicry as a causal mechanism in her first report. Pet. Ex. 7 at 4-5, 7. However, in her second report, she abandoned molecular mimicry because she was unable to find any common epitope between the hepatitis B vaccine and either the platelets or the red cells. Additionally, upon further consideration, she recognized that Evans syndrome involves antibodies attacking at least two blood cell lines – in this case, both platelets and red blood cells. She recognized that a single antigen in the hepatitis B vaccine was unlikely to have sequence homology with two blood cell lines. Pet. Ex. 16 at 1-2; *see also* Tr. 159-60, 63-64, 67. Indeed, respondent submitted a 2005 review article providing:

> Despite the frequency of haemopoietic cell-specific autoantibodies in patients with Evans syndrome, there is very little information about the identity of target antigens. Early work showed that the autoantibodies are specific to their target cells and as shown by absorption and elution, do not cross-react. (Pegels et al. 1982). Alterations in serum immunoglobulin levels in Evans syndrome have been reported in a number of studies but these are neither consistent or specific (Wang

[28] Citing R. McMillan, *The Pathogenesis of Chronic Immune Thrombocytopenic Purpura*, 44 Semin. Hematol. S3-11 (2007) [Pet. Ex. 28(j)]; D. Nugent et al., *Pathogenesis of Chronic Immune Thrombocytopenia: Increased Platelet Destruction and/ or Decreased Platelet Production*, 146 Br. J. Hematol. 585 (2009) [Pet. Ex. 28(m)].

> et al., 1983, Wang et al. 1988, Savasan et al. 1997) and the number of circulating B cells appears to be in the expected range (Pegels et al. 1982).[29]

Thus, Dr. Byers opined that there were "many proven mechanisms by which vaccines induce autoimmune diseases," including inflammation which releases inflammatory cytokines, antigen spreading, and binding of immune complexes. Pet. Ex. 16 at 2. In her conclusion, she simply indicated that she had "listed several accepted mechanisms of action by which vaccines/infections can induce ITP-Evans, and vaccines which can do it, including Hepatitis B." *Id.* at 3.

At the entitlement hearing and in her third, post-hearing expert report, Dr. Byers focused on bystander activation. Regarding this theory, she opined that autoreactive immune cells are present in every mammal. Pet. Ex. 27 at 1. They play a beneficial role in controlling growth and differentiation in all organ systems and normally, they are tightly controlled by regulatory immune cells. Pet. Ex. 27 at 1, 6-7.

Different immune cells are designed to protect against foreign antigens. The body's first line of defense, the innate immune system, is made up of cells that quickly identify the category of antigen presented (e.g., virus, bacterium, mold). The innate system can react quickly but with limited specificity. Pet. Ex. 27 at 1. It activates proinflammatory cytokines, which attract and recruit additional cells like macrophages and dendritic cells to aid in the inflammatory response. Pet. Ex. 27 at 1. The innate immune response eliminates the vast majority of the foreign antigen's load at this stage. Pet. Ex. 27 at 1. The proinflammatory cytokines also activate the adaptive immune system's B and T cells. Over the course of days or weeks, the B and T cells undergo genetic recombination and develop highly specific receptors that recognize the unique tertiary structure of the specific antigen presented. Pet. Ex. 27 at 1-2. After the antigen is fully cleared, the adaptive immune system retains long-term specific memory so that it can react more quickly to that specific foreign antigen if and when it presents again. Pet. Ex. 27 at 2.

Dr. Byers cited an article by Tough et al.[30] reporting that in mice infected with influenza virus, a cytokine called interferon 1 mediates the proliferation of T cells that are not specific to the flu. Pet. Ex. 27 at 2 (*citing* Pet. Ex. 28(n)). Upon activation and proliferation, the number of circulating T cells exceeds the number of viral cells. Pet. Ex. 28(n). Dr. Byers cited additional papers on the proposition that viral and bacterial infections can be associated with the over-proliferation of T cells. Pet. Ex. 27 at 2.[31] Dr. Byers opined that in individuals that have a

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[29] A. Norton & I. Roberts, *Management of Evans syndrome*, 132 Brit. J. Hematol. 125 (2005) [Resp. Ex. F], *citing* W. Wang et al., *Evans syndrome in Childhood: Pathophysiology, Clinical Course, and Treatment*, 10 Am. J. Ped. Haematol. 330 (1988) [Resp. Ex. H]; W. Wang et al., *Immunoregulatory Abnormalities in Evans syndrome*, 15 Am. J. Hematol. 381 (1983) [Resp. Ex. I]; S. Savasan et al., *Increased Lymphocyte Fas Expression and High Incidence of Common Variable Immunodeficiency Disorder in Childhood Evans syndrome*, 125 Clinical Immunology 224 (2007) [Resp. Ex. J].

[30] D.F. Tough, *Induction of Bystander T Cell Proliferation by Viruses and Type I Interferon in Vivo*, 272 Science 1947 (1996) [Pet. Ex. 28(n)].

[31] Citing G. Lertmemongkolchai et al., *Bystander Activation of CD8+T Cells Contributes to the Rapid Production of IFN-y in Response to Bacterial Pathogens*, 166 J Immunol. 1097 (2001); doi 10.4049/jimmunol.166.2.1097 [Pet.

genetic susceptibility, the introduction of a foreign antigen can activate dormant autoreactive T and B cells which trigger autoimmune disease.[32] Pet. Ex. 27 at 2.

Respondent's expert Dr. Gans criticized the theoretical nature of bystander activation saying that it had only been shown in vitro and argued that any stimulus could initiate the immune response. While it is not addressed in Dr. Byers's reports, following the hearing, petitioners also filed a study by van Aalst et al. published in 2017.[33] In this study, van Aalst et al. reported that bystander activation does not depend on strong T cell receptor (TCR) ligation, but on signals derived from the ongoing response directed against the vaccine antigen or adjuvant at hand. Pet. Ex. 29 at 1. They observed that in mice, the introduction of either adjuvanted or non-adjuvanted vaccine antigens was associated with a response specific to the vaccine as well as the bystander activation of non-vaccine-specific CD4+ T cells. Pet. Ex. 29 at 1, 6. Van Aalst et al. noted that their study did not demonstrate that the activated non-vaccine-specific cells had a functional effect. Pet. Ex. 29 at 7. They hypothesize that the immune system may have multiple checkpoints that prevent the activated cells from becoming functional. Additionally, epidemiologic evidence has not been shown. However, they indicate that bystander activation is one proposed mechanism by which vaccination might be involved in both acute and chronic autoimmune diseases. Pet. Ex. 29 at 1.

Dr. Byers relied on the Agmon-Levin article which validates the bystander activation theory as a biological mechanism because "enhanced cytokine production promotes the expansion of autoreactive T cells whose prior number had been insufficient to produce an overt disease." Pet. Ex. 27 at 3.[34] She said that each individual person has autoreactive T and B cells that are controlled by regulatory cells. Tr. 166; Pet. Ex. 27 at 3-4. However, some individuals have a genetic predisposition that can trigger these autoreactive T and B cells. Tr. 166; Pet. Ex. 27 at 3-4. The Atassi 2008 study, cited by Dr. Byers, provides scientific support that autoantibodies are known to exist and can be contributory in autoimmune diseases. Pet. Ex. 27 at 3-4.[35]

Dr. Byers opined that both infections and vaccines can cause bystander activation resulting in autoimmune diseases. Pet. Ex. 27 at 3-4. She stated: "In the case of polyclonal activation of B cells, the increased B cell proliferation, antibody production, and generation of

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Ex. 28(h)]; K. Murali-Krishna et al., *Counting Antigen-Specific CD8 T Cells: A Reevaluation of Bystander Activation during Viral Infection*, 8 Immunity 177 (1998) [Pet. Ex. 28(k)].

[32] A. Nogai, *Lipopolysaccharide Injection Induces Relapses of Experimental Autoimmune Encephalomyelitis in Nontransgenic Mice via Bystander Activation of Autoreactive* CD4 *+Cells*, 175 J Immunol. 959 (2005) [Pet. Ex. 28(l)]; B.J. Vilen & J.A. Rutan, *The regulation of autoreactive B cells during innate immune responses*, 41 Immunol Res. 295; doi: 10.1007/s12026-008-8039-8 (2008) [Pet. Ex. 28(o)]; Y.D. Dai et al., *Antigen Processing by Autoreactive B Cells Promotes Determinant Spreading*, 2 Cell. & Molec. Immunol. 169 (2005) [Pet. Ex. 28(e)].

[33] S. van Aalst et al., *Bystander activation of irrelevant CD4+T cells following antigen-specific vaccination occurs in the presence and absence of adjuvant*, 12 PLoS One; doi.org/10.1371/journal.pone.0177365 (2017). [Pet. Ex. 29].

[34] N. Agmon-Levin et al., *Influenza Vaccine and Autoimmunity*, 11 IMAJ 183 (2009) [Pet. Ex. 28(a) at 3].

[35] M. Zouhair-Atassi & P. Casali, *Molecular Mechanisms of Autoimmunity*, 41(2) Autoimmunity 123 (2008); doi 10.1080/08916930801929021 [Pet. Ex. 28(b) at 3-4].

circulating immune complexes also damages self-tissues. In the case of Evans syndrome, the major pathology was the buildup of antibodies on both platelets and red cells which were then removed by the spleen." Pet. Ex. 27 at 3. Thus, Dr. Byers opined that unlike molecular mimicry, bystander activation could cause an autoimmune response against two lines of blood cells as seen in Evans syndrome. Namely, bystander activation could activate autoreactive T and B cells directed against two lines of blood cells. *Id.*

Dr. Byers said that the innate immune system, in the initial response to the hepatitis B antigen, produces pro-inflammatory cytokines which then stimulate what she called rogue B cells and T cells that have different specificities. They attack the invader but then perceive that the platelets and red cells are also invaders and continue to attack. She agreed with respondent's experts that normally the regulatory cells would come in and tamp down the immune reaction once the invasion is eliminated but because of a likely genetic susceptibility in these children, it does not do so and the immune response then spins out of control.

While Dr. Byers focused on bystander activation, she opined that she was not "going to completely discount epitope spreading" or separately, "TLR activation" as part of the bystander activation process, as theories explaining how the hepatitis B vaccine can cause Evans syndrome. Tr. 160-61. Indeed, even following my post-hearing order requesting supplemental reports to clarify the experts' opinions, Dr. Byers concluded: "my opinion as to the cause of the Evans (ITP and hemolytic anemia) syndrome would remain – the [hepatitis B] vaccine was a cause or substantial contributory factor, and the mechanism of action was *either by bystander activation or epitope spreading.*" Pet. Ex. 27 at 5 (emphasis added). However, epitope spreading was not particularly explained by Dr. Byers or summarized in petitioners' pre- or post-hearing brief. This appeared to be a supplemental theory that was not sufficiently detailed to be evaluated. Thus, I have not endeavored to summarize that additional theory to the extent that it was offered in this case.

4. Dr. Byers's Opinion Regarding Sequence of Cause and Effect and Timing

Dr. Byers opined that D.B. was perfectly healthy before receiving the hepatitis B vaccine (and Prevnar). He developed the first manifestations of Evans syndrome approximately eight days later, which progressed rapidly over the next three days. Dr. Byers opined that certain vaccinations are known to trigger certain autoimmune conditions. In D.B.'s case, she did not identify any alternative causes such as infection. Thus, she concluded that there was a logical sequence of cause and effect. She also believed that there was an acceptable temporal relationship. Tr. 113-14.

C. Respondent's Expert Dr. Hayley Gans

1. Dr. Gans's Qualifications

Respondent submitted two reports and testimony from Dr. Gans. Resp. Ex. D; Tr. 209-341; Resp. Ex. W (post-hearing). She obtained a bachelor's degree in biochemistry from Connecticut College in 1987 followed by a M.D. from the SUNY Health Science Center at Syracuse in 1991. Resp. Ex. E. Dr. Gans then completed an internship and residency in Pediatrics at Stanford University School of Medicine, followed by a fellowship in Pediatric

Infectious Diseases at Stanford. *Id.* at 1. Dr. Gans is board certified in Pediatrics and Pediatric Infectious Diseases. Tr. 212. She explained that there is a board for allergy/immunology, in which she did not do a residency. There is not a stand-alone board for immunology. *Id.* Dr. Gans is currently an Assistant Professor of Pediatrics at Stanford. Resp. Ex. E at 2. She works as a consultant in pediatric infectious disease. Tr. 213. She has treated children with ITP, CVID, and Evans syndrome, and she has diagnosed both CVID and Evans syndrome. Tr. 213-18. I admitted Dr. Gans as an expert in pediatrics, pediatric infectious diseases, immunology, and vaccines insofar as all of those subjects relate to Evans syndrome. *Id.* at 216, 220.

2. Dr. Gans's Opinion Regarding Evans syndrome

Dr. Gans, like all of the other experts in this case, agreed that D.B's correct diagnosis is Evans syndrome. Resp. Ex. D at 2; Tr. 222-23. She acknowledged that there was currently no genetic test for this condition. Tr. 298. She agreed that the diagnosis depends on a finding of decreased counts in at least two blood cell lines, a positive Coombs- or direct-antibody test, and the exclusion of other immune conditions. She opined that Evans syndrome is a very rare condition that is still being studied, but that the current limited understanding of this condition is relevant to the likelihood of vaccine causation. *See, e.g.*, Resp. Ex. D at 2; Tr. 222-23.

Dr. Gans opined that children with Evans syndrome have clinical similarities with other immunodeficiencies but their immune systems act differently. Either acute ITP or hemolytic anemia, presenting alone, generally responds to first-line treatments and resolves within months to a year. Tr. 249; Resp. Ex. W at 2. Dr. Gans allowed that these conditions may require a trigger. *See, e.g.*, Resp. Ex. W at 4, 5.

In contrast, Evans syndrome does not respond to the same first-line treatments and is chronic and relapsing. Tr. 249; Resp. Ex. W at 2. Additionally, some children with Evans syndrome go on to develop other immune conditions such as common variable immune disorder ("CVID") and autoimmune lymphoproliferative syndrome ("ALPS"). Resp. Ex. D at 2; Tr. 224.

In recognition of the more difficult course of Evans syndrome, scientists are currently working to understand its pathophysiology. Tr. 226-27.

By way of introduction, Dr. Gans explained that the immune system, when functioning typically, should recognize a foreign antigen, respond effectively to eliminate the foreign antigen, and then dampen the response and return the body to homeostasis. Tr. 230; Resp. Ex. W at 5. She described that this occurred through a regulatory pathyway in which activated immune cells express a cell surface protein called Fas ligand, which is recognized by T cells that possess a cell surface protein called Fas. When the Fas and Fas ligand cells combine, the activated immune cells die (termed apoptosis), the immune response ceases, and the body returns to homeostasis. Tr. 231; Resp. Ex. W at 2.

Dr. Gans opined that dysfunction in this regulation of the immune system explains Evans syndrome. There are very few patients diagnosed with Evans syndrome. However, when studied, those patients seem to have inherent defects or irregularities in the immune system, including T and B cells. Resp. Ex. D at 2; Resp. Ex. W at 1. For example, a study by Wang et

al.[36] found that subjects with Evans syndrome showed increased T suppressor cells and decreased T helper cells. The subjects had a markedly decreased T4:T8 cell ratio. When compared to subjects with chronic ITP, the subjects with Evans syndrome had no significant difference in T4 but they had a higher percentage in T8 and a lower T4:T8 ratio. Additionally, among the six subjects with Evans syndrome, two subjects had diminished IgG, five subjects had diminished IgA, and two subjects had diminished IgM. Resp. Ex. D at 2 (citing to Resp. Ex. H at 1).

Dr. Gans connected these findings to a possible defect in the Fas-Fas ligand pathway in patients with Evans syndrome. She cited a study by Teachey et al., [37] which found that 58% (7/12) of patients with Evans syndrome also had ALPS.[38] Additionally, 50% (6/12) had defective Fas-mediated apoptosis. *Id.* Teachey et al. described Fas-mediated apoptosis as part of the normal down regulation of the immune system.[39] They describe the keynote finding in ALPS is a disorder of T cell dysregulation caused by defective Fas mediated apoptosis.[40] Teachey et al state:

> Autoimmune lymphoproliferative syndrome (ALPS) is a disorder of disrupted lymphocyte homeostasis caused by defective Fas-mediated apoptosis. As part of the normal down regulation of the immune response, activated T lymphocytes upregulate expression of Fas ligand. (Nagata and Golstein, (1995). Fas and Fas ligand interact through the Fas-activating death domain (FADD) to trigger the caspase cascade, leading to proteolysis, DNA degradation, and apoptosis. Patients with ALPS have a defect in this apoptotic pathway, leading to chronic lymphoproliferation and autoimmune manifestations.

Resp. Ex. BB at 205.

Teachey et al. also found that no patient with ITP or autoimmune hemolytic anemia alone had both double negative T cells and defective Fas-mediated apoptosis, which is the criteria for ALPS. Two patients with ITP were described with defects in Fas-mediated apoptosis but did not have double negative T cells. Resp. Ex. K at 2447. Teachey et al. went on to say that autoimmunity is the second most common clinical manifestation of ALPS after lymphoproliferation with autoimmune destruction of blood cells being the most common presentation of autoimmunity in ALPS, affecting over 70% of patients. Resp. Ex. BB at 2.

Teachey et al. noted: "[L]aboratory testing [of the Fas-Fas ligand pathway] is labor-intensive and expensive to perform, requiring multiple controls, including positive and negative controls from both the patient and a normal control to be analyzed in tandem. Accordingly, it is

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[36] W. Wang et al., *Immunoabnormalities in Evans syndrome,* 15 Am J. Hematol. 381 (1983) [Resp. Ex. H].

[37] D.T. Teachey et. al, *Unmasking Evans syndrome: T-cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS),* 105 Blood 2443 (2005) [Resp. Ex. J].

[38] D.B. has never been diagnosed with ALPS.

[39] D.T. Teachey et al., *Advances in the management and understanding of autoimmune lymphoproliferative syndrome (ALPS),* 148 Br. J. of Haematol. 205 (2009) [Resp. Ex. BB].

only performed in a handful of research laboratories in the world." Resp. Ex. BB at 4.

Dr. Gans also cited a study by Savasan et al.[41] on seven patients with Evans syndrome followed over five years. Seventy-one percent (5/7) developed CVID. Those patients displayed an *increased* expression of Fas-antigen on B lymphocytes and *increased* Fas-mediated apoptosis, resulting in the decreased level of antibodies in patients with CVID. Resp. Ex. J at 225. The five patients who went on to develop CVID had increased spontaneous lymphocyte Fas expression and enhanced Fas-mediated apoptosis. *Id.* These findings were suggestive of persistent immune activation in some patients with Evans syndrome. *Id.* Savasan also noted that previous research concluded that up to 11% of patients with CVID may develop some form of autoimmune blood disorder including Evans syndrome. However, as demonstrated in the study by Savasan et al., Evans syndrome may *precede* development of the CVID phenotype. Pet. Ex. J at 5.

Like the other experts, Dr. Gans discussed the presence of CVID in D.B. In her first report, she opined that "D.B. developed Evans syndrome as part of an underlying immunodeficiency which was eventually defined as [CVID]." Resp. Ex. D at 3. But she also acknowledged that D.B.'s treating physicians never made that diagnosis and that it is extremely difficult to diagnose in young children. Tr. 271-72, 294 (discussing Pet. Ex. 26). Dr. Gans opined that D.B. is receiving IVIg for hypogammaglobulinemia, which is the treatment for CVID. Tr. 272. It is interesting to note that multiple authors including Norton say that the first line treatment for Evans syndrome is IVIg. Resp. Ex F at 128. Despite this debate over whether D.B. has CVID, in Dr. Gans's last report, she stated that "the presence or absence of CVID in D.B. is not important for casualty [sic; presumably "causality"], but as with ALPS, represents an entity that appears to develop over time in some individuals who carry a diagnosis of Evans syndrome." Resp. Ex. W at 4.

Dr. Gans explained why Teachey and Savasan reported different findings in the context of Evans syndrome:

> In summary, at the core of the immune issue in individuals with Evans syndrome is a defect in the regulation of immune activation, and this is in part through defects expressed in the Fas-Fas ligand pathway. This leads to (1) the incomplete destruction of activated cells that are recognizing self and the production of autoantibodies against the cells of the hematopoietic system which are most vulnerable to these dysregulated cells *[resulting in ALPS, as reported by Teachey et al.]* and (2) an overstimulated immune state due to inability over time to deactivate the system which in turn creates the body to produce more immune cells, and the cells produced in the B lymphocyte category than express Fas ligand (given the high numbers this level is observed to be higher) and are cleared leading to hypogammaglobinemia and CVID *[as reported by Savasan et al.]* This may seem paradoxical, but is observed in immune-activated states since the body is making more cells in an attempt to correct the defect and some of these are defective giving rise to (1) and some are not defective but over-expressed giving

[41] S. Savaşan et al., *Increased lymphocyte Fas expression and high incidence of common variable immunodeficiency disorder in childhood Evans syndrome*, 125 Clin. Immunol. 224 (2007) [Resp. Ex. X].

rise to (2).

Resp. Ex. W at 2-3; *see also* Tr. 232. Dr. Gans also allows that the immune regulatory system "has been an area of active investigation for years and is not entirely understood," and its "complexity . . . is phenomenal." Resp. Ex. W at 3.

Dr. Gans opined that while Evans syndrome is rare, the hematopoietic (blood) system is in fact the most common location for autoimmunity to occur. Resp. Ex. W at 3. "Likely this represents the fact that the endovascular (or circulatory system) plays an important role in preventing autoimmunity." *Id.* More specifically:

> It is believed that in individuals with immune dysregulation, the abnormal immune cells (such as B and T cells with abnormalities in the Fas ligand system, such as with Evans syndrome) circulate in the blood but the intravascular surfaces act as a barrier preventing these dysregulated cells from entering other tissues and thus in turn preventing broad tissue autoantibodies. In contrast, the intravascular antigens (red cells and platelets) remain exposed to the dysregulated immune cells, causing autoimmunity to be directed at these cells more commonly.

Id. at 3-4.[42]

Dr. Gans opined that individuals develop Evans syndrome as a result of the inherent defects in the immune regulatory system discussed above. She opined that this pathophysiology does not include an external antigenic stimulation as a source for the autoimmune phenomenon associated with the disorder. Anything – a virus, an infection, or "the Grandma's kiss" – can conceivably stimulate the immune system. Tr. 262. However, the key failure and cause of Evans syndrome is that once the antigen is cleared, the immune cells are not cleared from the body and they look for something else to attack, and the blood cells are most vulnerable to that attack. Tr. 298-99.

Dr. Gans acknowledged that in her patients diagnosed with Evans syndrome, when they get an infection, "their syndrome definitely gets worse." However, she did not take that to mean that an infection or other specific antigen is necessary for Evans syndrome to develop. Tr. 262; *see also* Tr. 266, 298-99, 303; Resp. Ex. W at 6.

3. Dr. Gans's Opinion Regarding Causation between the Hepatitis B Vaccine and Evans syndrome

Dr. Gans conceded that a vaccine could trigger an adaptive immune response. Tr. 277, 320. However, as discussed above, she opined that a foreign antigen such as a vaccine is not the cause of Evans syndrome. Rather, the cause is the failure to clear the immune response once the foreign antigen is cleared.

[42] Citing J.C. Turbyville & V.K. Rao, *The Autoimmune Lymphoproliferative Syndrome: A Rare Disorder Providing Clues about Normal Tolerance*, 9 Autoimmun. Rev. 488 (2010) [Resp. Ex. AA].

Dr. Gans acknowledged that there has been one case report associating Evans syndrome with hepatitis B vaccine[43] and another associated with hepatitis B infection.[44] Resp. Ex. D at 3. However, she opined: "These cases are less likely to represent true Evans syndrome since the cytopenias in these cases were very responsive to first-line therapies which is not the case for true Evans syndrome." *Id.*[45]; *see also* Tr. 265-67.

4. Dr. Gans's Opinion Regarding Sequence of Cause and Effect

Dr. Gans opined that D.B. would have developed Evans syndrome at some point during his childhood independent of the vaccine. Resp. Ex. D at 4. As discussed above, Dr. Gans opined that Evans syndrome is not caused by an immune response to a vaccination; but instead it is the failure of the immune system to deactivate that causes Evans syndrome. Resp. Ex. W at 2.

5. Dr. Gans's Opinion Regarding Timing

In contrast to petitioners' experts, Dr. Gans concluded retrospectively that D.B's first manifestations of Evans syndrome were recorded three days after the hepatitis B vaccination. Resp. Ex. D at 3. She opined that D.B.'s irritability was "likely [his] usual reaction to vaccines," based on his earlier history. *Id.* However, based on her retrospective knowledge of his later diagnosis of Evans syndrome, she characterized the mark on the pinna of his ear as "bruising." *Id.* She opined: "[T]he bruising on the pinna with manipulation and at the site of his immunization is suggestive of low platelets. At this point, the platelet count was not likely low enough to result in the spontaneous bruising that subsequently developed on [D.B.'s] body but would be at a level that trauma would be required to cause bruising." *Id.* Dr. Gans opined that these symptoms were too soon after the vaccination to infer causation. *Id.*; Tr. 265.

D. Respondent's Expert Dr. Joan Cox Gill

1. Dr. Gill's Qualifications

Respondent submitted one expert report and testimony from Dr. Gill. Resp. Ex. A; Tr. 342-407. She obtained a bachelor's degree in science from St. Norbert College in 1965 followed by an M.D. from the Medical College of Wisconsin in 1976. Resp. Ex. B. Dr. Gill then completed an internship and residency in Pediatrics at Milwaukee Children's Hospital, followed by a fellowship in Pediatric Hematology-Oncology at the Medical College of Wisconsin and the Blood Center of Southeastern Wisconsin. *Id.* at 1. Dr. Gill was board certified in Pediatrics and Pediatric Hematology/Oncology. Tr. 244; Resp. Ex. B at 4. At the time of the hearing, Dr. Gill was a Professor of Medicine, Pediatrics, and Population Health – Epidemiology at the Medical College of Wisconsin, and an Investigator at the Blood Center of Southeastern Wisconsin. Resp.

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[43] E. Martinez & P. Domingo, *Case Report: Evans syndrome Triggered by Recombinant Hepatitis B Vaccine*, 15 Clinical Infectious Diseases 1051 (1992) [Resp. Ex. P].

[44] A. Kalayci et al., *Case Report: Evans syndrome Related to Hepatitis B Virus Infection: A Case that Responded to Lamivudine Therapy*, 32 J. Ped. Gastro. & Nutrition 493 (2001) [Pet. Ex. 25].

[45] Citing P. Mathew et al., *Evans syndrome: Results of a National Survey*, 19 J. Ped. Hem. Oncol. 433 (1997) [at Resp. Ex. C at 1-5].

Ex. B at 2. Dr. Gill has worked with patients with ITP and autoimmune hemolytic anemia, among other blood disorders. Tr. 346. She diagnosed and treated four or five cases of Evans syndrome in her career, and she treated two patients who went on to develop the manifestations of CVID, though she did not diagnose those patients. Tr. 346, 351. I admitted Dr. Gill as an expert in pediatrics, hematology, and immunology insofar as those topics relate to Evans syndrome. Tr. 347, 351.

2. Dr. Gill's Opinion Regarding Evans syndrome

Dr. Gill opined that there is good evidence that the MMR vaccine (not at issue in this case) causes ITP. In fact, this has been added to the Vaccine Injury Table. Tr. 349. With regard to the hepatitis B vaccine, almost all of the literature consists of case reports and those are almost all consistent with *acute* opposed to *chronic* ITP. Tr. 349-50.

Dr. Gill opined that acute ITP is probably caused by an antigen (for example, an upper respiratory infection) triggering an immune response which then cross-reacts with platelets. As the immune system clears that antigen, the antibody response goes away. The ITP subsides and does not recur. Tr. 350.

Dr. Gill opined that in contrast, chronic ITP and by extension, Evans syndrome does not have a precipitating event. Dr. Gill testified, consistently with Dr. Gans, that in a patient destined to develop one of these conditions, once the immune system is stimulated, it never turns off. The response is not regulated and the system does not return to homeostasis. Once the trigger is eliminated, the immune system attacks self. Dr. Gill opined that the immune stimulant can be many things – possibly including inhaled air, or food. Tr. 383-85. When asked whether a cold or virus could serve as that trigger, she said no. However, a cold or virus could suppress the bone marrow, causing the patient's platelet count to drop so low that he would become symptomatic. Tr. 386-87. Dr. Gill then had the following exchange:

> Petitioners' counsel: All right. So the cold could have been the insult that caused the - -
> A: The manifestation - -
> Q: - - the Evans to be - -
> A: of the disorder.
> Q: But in this case there was no cold.
> A: No, right, yeah, but that's - - you know - -
> The Court: But by the same token, could the vaccine be enough to suppress the bone marrow?
> A: You know, I don't know. I think it's a really good question, I think it's a possibility, but I honestly don't know the answer to that.

Tr. 387-88. Additionally, in response to my questioning, Dr. Gill stated that she did not know why the immune system, once stimulated by a foreign antigen and not regulated back down, attacks specifically the two blood cell lines. She also did not know why in some patients the attack on both cell lines began simultaneously and in others they are attacked sequentially. Tr. 388-90.

3. Dr. Gill's Opinion Regarding Causation between the Hepatitis B Vaccine and Evans syndrome

In terms of the mechanisms of the immunology in Evans syndrome, Dr. Gill testified that the Hepatitis B vaccine has a single antigen, the hepatitis B surface antigen. Tr. 356. The antibody that would attach to this antigen would also have to attach to both the platelets and the red cells. But she testified that it has been clearly shown that the antibodies that are present on the platelets do not bind to the red cells and vice versa. Tr. 357.

Dr. Gill indicated that she generally would like to see epidemiology to draw conclusions about causation. She observed that the Vaccine Adverse Events Reporting System (VAERS) is voluntary and the cases are not fully worked up; nonetheless, VAERS data may sometimes provide a signal.

She agreed with the other experts that Evans syndrome is a very rare disease. She did an interesting calculation on the witness stand that demonstrated the difficulty with epidemiology in rare diseases. Specifically, the incidence of ITP is about 1.5 per 100,000 children and Evans would be about 1 in 10,000,000 (ten million) children. Therefore, a study would need at least a million children to pick up one case of Evans syndrome. Thus, respondent's submitted study by O'Leary et al.[46] in the Journal of Pediatrics, evaluating the risk of ITP after vaccination based on data from 1.8 million children and adolescents, was not sufficiently powered to draw any conclusions. Tr. 405-06.

Dr. Gill generally agreed with Dr. Gans that there was not a logical sequence of cause and effect or an acceptable temporal relationship in D.B.'s case. Thus, her opinions on those topics will not be repeated here.

IV. DISCUSSION

A. *Althen* Prong One

1. Legal Standard

Under *Althen* prong one, the causation theory must relate to the injury alleged. Thus, a petitioner must provide a "reputable" medical or scientific explanation, demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006) (citations omitted). The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). It must only be "legally probable, not medically or scientifically certain." *Id.* at 549.

In *Althen*, the Federal Circuit noted that "while [that petitioner's claim] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, *a sequence hitherto unproven in medicine*, the purpose of the Vaccine Act's preponderance standard is to

[46] S.T. O'Leary et al., *The Risk of Immune Thrombocytopenic Purpura after Vaccination in Children and Adolescents*, Pediatrics (2012), doi: 10.1542/peds.2011-111 [Resp. Ex. R].

allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body." Althen,* 418 F.3d at 1280 (emphasis added). Accordingly, the first *Althen* prong may be satisfied without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu*, 569 F.3d at 1378-79 (citing *Capizzano*, 440 F.3d at 1325-26)). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not from the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Human Servs.*, 121 Fed. Cl. 230, 245 (2015), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017). But this does not negate or reduce a petitioner's ultimate burden to establish his overall entitlement to damages by preponderant evidence. *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted).

2. Evans syndrome

As summarized by Drs. Forman and Gans, Evans syndrome (ES) is an autoimmune disorder characterized by hemolytic anemia, thrombocytopenia and often neutropenia which can occur simultaneously or sequentially. It was first reported in 1951 but continues to be a disorder that is not well understood. With the exception of two,[47] almost all of the studies submitted in this case[48] included very small numbers of patients reflecting the rarity of the disease. Even with such small numbers, there was also significant variation in the presentations.

Ages of patients ranged from the first year of life to well into adulthood. For example, Wang[49] reported on ten patients with onset ranging from nine to fifteen years old with a median of 7.5 years old. In a separate study, Mathew et al.[50] reported on 42 patients with onset ranging from 2 months to 26 years old, with a median of 7.7 years old.

The typical presentation varies. For example, in Mathew's study of 42 patients, at their initial presentation, 32 had ITP, 28 had hemolytic anemia, 10 had neutropenia and 6 had pancytopenia. Resp. Ex. Q.

The subsequent course also varies. For example, Wang et al. found that 7 out of 10 patients had recurrences of hemolytic anemia (up to 22 episodes total). Nine out of 10 patients had recurrences of thrombocytopenia (up to 20 episodes total). Resp. Ex. Y at 5.

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[47] P. Mathew et.al. (1997) [Resp. Ex. Q] (42 patients in the United States and Canada); N. Aladjidi et al. (2011) [Pet. Ex. 21(f)] (265 patients in France).

[48] *See, e.g.*, W. Wang (1988) [Resp. Ex. H] (10 patients); W. Wang et al. (1983) [Resp. Ex. I] (6 patients). S. Savasan (2005) [Resp. Ex. X.] (7 patients); D. Teachey et al. (2005) [Resp. Ex. Y] (12 patients).

[49] W. Wang (1988) [Resp. Ex. H].

[50] P. Mathew et.al. (1997) [Resp. Ex. Q].

Furthermore, it appears that Evans syndrome sometimes presents as part of a separate autoimmune disease – most frequently systemic lupus erythematosus (SLE). This is not considered a true Evans syndrome.[51]

Both parties' experts agreed that Evans syndrome is generally chronic and involves exacerbations and remissions with response to treatment being variable even within individual patients having the need to resort to second and third line treatments. *See, e.g.*, Tr. 65-67 (Dr. Forman), 226-27 (Dr. Gans). Evans syndrome is usually treated first with steroids and/or IVIg. Second and third line treatments include various immunosuppressants, chemotherapy, splenectomy and stem cell transplants. All appear to have variable rates of success with splenectomy falling out of favor as the improvement tends to be short-lived.

The enormous variability in Evans syndrome, particularly the onset ranging from infancy to adulthood, raises the question of whether a trigger is needed. This may have been the principal debate between the parties' experts in this case. Respondent's expert Dr. Gans argued, and Dr. Gill agreed, that Evans Syndrome is generally considered to be caused by a defective immune regulatory system which will develop at some point in life regardless of a specific trigger. Dr. Forman and Dr. Byers seemed to agree that Evans syndrome involves a failure of the immune regulatory system but contended that a trigger was necessary.

As noted in a relatively recent review article by Norton et al.,[52] there have not been studies on whether there is any association between vaccination and Evans syndrome. There *have* been articles associating vaccination (and infection) with the development of hemolytic anemia or ITP (in separate cases). Norton provides: "Taken together these reports suggest that immunizations may provide a trigger for the development of disease in susceptible individuals and may also lead to a sustained increased risk in some of them." Resp. Ex. F at 2. Thus, petitioners' expert Dr. Byers tried to analogize hemolytic anemia and ITP, as each presents on its own, to Evans syndrome. She recognized a distinction between acute ITP (which is monophasic and generally resolves within a short period of time) and chronic ITP (which is recurrent and more resistant to treatment). However, she seemed to contend that chronic ITP could be similar to Evans syndrome, except that the latter would involve two cell lines. Pet. Ex. 16 at 3-4; Pet. Ex. 27 at 3.

Dr. Gans contended that Evans syndrome is unique. She noted that compared to ITP and hemolytic anemia, Evans syndrome is associated with "increased expression of Fas on both B and T cell lymphocytes with higher Fas-induced activated T lymphocyte apoptosis." Resp. Ex. D at 1.[53] Dr. Gans also recognized that there are cases of chronic ITP. Resp. Ex. D at 1. However, she maintained that compared to chronic ITP, Evans syndrome had a distinctive profile including "increased T suppressor and decreased T helper cells and subsequent diminished Ig production." Resp. Ex. D at 2.[54] Dr. Gans also found it more significant that ITP

[51] W. Wang (1988) [Resp. Ex. H]; D. Teachey et al. (2005) [Resp. Ex. Y]

[52] A. Norton & I. Roberts (2005) [Resp. Ex. F].

[53] Citing S. Savasan (2005) [Resp. Ex. X.]; D. Teachey et al. (2005) [Resp. Ex. Y].

[54] Citing W. Wang et al. (1983) [Resp. Ex. I].

involves one cell line and Evans syndrome involves two cell lines. Therefore, although Dr. Gans agreed that ITP (at least the acute form) may be the result of an autoimmune response to an antigen, she opined that ITP was dissimilar to Evans syndrome. Resp. Ex. D at 1-2; Resp. Ex. W at 1-2. However, her distinction between Evans syndrome and chronic ITP was not as clear and she acknowledged that at least some cases of chronic ITP had at least some of the same immune pathways occurring with Evans syndrome. Tr. 268-69.

As discussed above and repeated here because of the significance to the case, Dr. Gans opined that Evans syndrome is the result of immune dysregulation. A normal immune system can mount an effective response eliminating a foreign antigen, but afterwards, Fas and Fas ligand surface proteins connect and cause apoptosis, ending the immune response and returning the system to homeostasis. However, studies suggest that in patients with Evans syndrome, the Fas-Fas ligand pathway is aberrant, leading to an attack on the self. Tr. 231-32; Resp. Ex. W at 2-3, 5. Dr. Gans also opined that while Evans syndrome is rare, the hematopoietic (blood) system is in fact the most common location for autoimmunity to occur. Resp. Ex. W at 3. "Likely this represents the fact that the endovascular (or circulatory system) plays an important role in preventing autoimmunity." *Id.*

As discussed above, Evans syndrome (requiring low counts in two blood cell lines) can overlap with either ALPS (requiring the presence of double negative T cells and defective Fas-mediated apoptosis; *see* studies by Teachey et al.) or CVID (requiring low counts in two gammaglobulin lines, sometimes including attacks on the blood cells, *see* studies by Savasan et al.).[55] These findings appear at least somewhat paradoxical. Indeed, a review of the literature and the expert testimony suggests that Evans syndrome is not fully understood. The medical community and the experts in this case agree that in Evans syndrome, the two different cell lines (i.e., the red blood cells and platelets) are being attacked by different immune cells which are not cross-reactive.[56] The available studies suggest that it is quite likely that Evans syndrome involves a defect in the regulatory arm of the immune system, possibly involving a defect in the Fas-Fas ligand pathway which can manifest in several different ways. First, a failure in Fas-mediated apoptosis may result in chronic lymphoproliferation. In other patients, an enhanced Fas-mediated process may result in decreased B and T cells. The authors of these studies also consistently say that the etiology of Evans syndrome is unknown.[57] For example: "Although

[55] In this case, the experts devoted significant time debating whether D.B. developed CVID and whether that was the cause or residual effect of his Evans syndrome. Petitioners' expert Dr. Byers initially opined that he had CVID which has many manifestations including hemolytic anemia, ITP, and "ITP-Evans." Pet. Ex. 7 at 2-3. But over the course of litigation, she amended that opinion. Later, Dr. Byers – and Dr. Forman - observed that D.B.'s gammaglobulin levels were normal at the outset of his disease and that subsequent tests could not be read accurately because he was receiving infusions of gammaglobulin by way of IVIg treatment. Additionally, there is no indication that D.B. was ever tested for abnormalities in the Fas-Fas ligand pathway. Pet. Ex. 27 at 5-6. Respondent's expert Dr. Gans continued to suspect that D.B. had CVID. However, she opined that "the presence or absence of CVID in D.B. is not important for casualty [sic; presumably "causality"], but as with ALPS, represents an entity that appears to develop over time in some individuals who carry a diagnosis of Evans and are followed over time." Resp. Ex. W at 4. Thus, I will not make a determination whether or not D.B. developed CVID.

[56] *See, e.g.*, A. Norton & I. Roberts (2005) [Resp. Ex. F at 2].

[57] A. Norton & I. Roberts (2005) [Resp. Ex. F at 1].

Evans syndrome appears to be a disorder of immune regulation, the exact pathophysiology is unknown. Most studies have involved small numbers of patients . . . However, taken as a whole, there is evidence to support abnormalities in both cellular and humoral immunity in Evans syndrome."[58] And: "The etiology of Evans remains speculative at this time. Wang et al. noted abnormalities of lymphocyte subsets and immunoglobulin synthesis, supporting the concept of aberrant immunoregulation in this condition."[59] Alterations in serum immunoglobulin levels in Evans syndrome have been reported in a number of studies, but these are neither consistent nor specific. Moreover, the number of circulating B cells appears to be in the expected range.[60] The literature appears to be in agreement that the underlying pathology of Evans syndrome is unknown but respondent's experts suggest that Evans occurs because of the failure of the immune system to regulate itself resulting in multiple dysregulated pathways with the end result being autoimmune damage to different cell lines circulating in the blood where the cells are most exposed to autoimmune attack.

The literature on Evans, for the most part, does not examine the potential role of triggers. It is unclear why the studies do not examine potential triggers for onset of Evans syndrome; however, it is clear that the pathophysiology of the disease is not entirely apparent.

Even if the conclusion is that the disease is solely a function of regulatory failure, it is not at all clear why that failure in some instances results in depressed immune cells, in others excessive lymphocytes and in others is simply described by damage to the platelets and red cells with different antibodies on the cells. It is not clear why if the immune cells are depressed, they continue to attack the platelets and red cells. Nor is it clear why the onset of the disease occurs at such varying ages, although Dr. Gans theorized that this is just a function of different maturational processes of the immune system. Tr. 259.

3. Bystander Activation

As summarized above, Dr. Byers's initial opinion was that molecular mimicry between the hepatitis B vaccine and the self can cause Evans syndrome.

Dr. Byers then recognized that Evans syndrome involves reduced counts in two separate cell lines which are attacked by different autoantibodies that do not cross-react.[61] She acknowledged that it was unlikely for the hepatitis B vaccine, having only a single antigen, to have sufficient similarity with both cell lines to result in molecular mimicry with two separate cell lines. Tr. 163-64. She did maintain that they were "fairly closely related cells of the hematopoietic lineage." Tr. 165.

Dr. Byers shifted her focus to a theory of bystander activation, which is discussed in more detail above. Put simply, bystander activation depends on a foreign antigen entering the

[58] A. Norton & I. Roberts (2005) [Resp. Ex. F at 2].

[59] P. Mathew et.al. (1997) [Resp. Ex. Q at 1].

[60] A. Norton & I. Roberts (2005) [Resp. Ex. F at 2], citing to W. Wang (1988) [Resp. Ex. H]; W. Wang et al. (1983) [Resp. Ex. I]; other citations omitted as not filed in this case.

[61] *See* A. Norton & I. Roberts (2005) [Resp. Ex. F].

body and activating the non-specific innate immune system, which releases non-specific inflammatory cytokines, which activate dormant B and T cells directed against part(s) of the self. Specific to this case, Dr. Byers opined that a hepatitis B vaccine can activate the immune system to attack the hepatitis B antigen, but also activate bystander immune cells which attack the red blood cells and platelets.

4. Conclusion on *Althen* Prong One

While bystander activation is a recognized theory of autoimmunity that has been proposed by many authors, I could find no reference to it in any of the literature regarding Evans syndrome. While the pathophysiology of Evans syndrome appears to be far from certain and not completely understood, it does appear that the predominant thinking does not implicate the activation of previously dormant autoreactive cells that produce antibodies specific to the blood cells. Rather, the predominant thinking focuses on malfunction of the regulatory system. The most recent submitted studies on Evans syndrome and related conditions are by Teachey et al. documenting a subgroup of twelve patients expressing *resistance* to Fas-mediated apoptosis leading to ALPS,[62] and by Savasan et al. documenting a subgroup of seven patients expressing *increased* Fas-activated lymphocyte apoptosis leading to CVID.[63] Thus, the focus of the Evans literature has been almost entirely on the regulatory arm of the immune system and not on the effector side of it.

Bystander activation or other types of autoimmune activation as triggering mechanisms for Evans syndrome were generally not discussed in the literature on Evans syndrome. Norton et al. do reference that a number of authors have investigated the role of various childhood immunizations in the development of *ITP* or *hemolytic anemia*. Norton et al. provide that: "Taken together, these reports suggest that immunizations may provide a trigger for the development of disease in susceptible individuals and may also lead to a sustained increased risk in some of them." However, Norton et al. also make clear that none of these studies was on *Evans syndrome*.[64] Petitioners submitted one case study on the onset of Evans syndrome following hepatitis B vaccine[65] and another following hepatitis B virus,[66] but these do not explain the multiplicity of antigens that would be required or address the problem of chronicity in Evans as opposed to the most common forms of ITP and hemolytic anemia. To wit, in the case involving the hepatitis B vaccine, the patient (a 33-year-old man with bone marrow-documented erythroid hyperplasia and megakaryocytic thrombocytopenia) had a good recovery after two months treatment with methylprednisolone. Resp. Ex. P at 1.

At this point, a role for vaccines as triggers in this puzzling and very rare disease cannot be entirely discounted. However, the evidence presented in this case is insufficient to establish a

[62] D. Teachey et al. (2005) [Resp. Ex. K, also filed as Resp. Ex. Y]; *see also* D. Teachey et al. (2009) [Resp. Ex. BB].

[63] Savasan (2007) [Resp. Ex. J, also filed as Resp. Ex. X].

[64] A. Norton & I. Roberts (2005) [Resp. Ex. F at 2].

[65] E. Martinez & P. Domingo (1992) [Resp. Ex. P].

[66] A. Kalayci et al. (2001) [Pet. Ex. 25].

reliable theory in the face of the dominant thinking in the literature to the effect that an activation of the immune system causing an elevation of immune cells is not counteracted after the threat has been eliminated and the system returned to homeostasis.

It appears that the leading theory is this inherent failure of immune regulation that allows the multifaceted attack on different elements of the hematologic system, in this case the platelets and red cells simultaneously. While Dr. Byers demonstrated through the literature general theories of autoimmunity, which could conceivably play a role in this disease, Dr. Gans was better able to tie the analysis of this rare syndrome to the research that has been done on the disease itself and to explain its implication for treatment of patients with the condition whom she manages. Although the mechanism or pathophysiology is far from certain and the studies to date have produced paradoxical results, leaving many questions about the cause of the disease, the research does focus on the regulatory arm of the immune system and does not appear to have addressed theories like bystander activation to explain this difficult and chronic disease.

Accordingly, I have concluded that the evidence of bystander activation is too speculative to establish a theory of vaccine causation in the face of the *relatively* defined theory of immune dysregulation in this case. Accordingly, petitioners have not carried their burden to establish by a preponderance of the evidence that bystander activation is a theory under which the hepatitis B vaccine can cause Evans syndrome, accordingly, the claim fails *Althen* prong one.

B. *Althen* Prong Two

1. Legal Standard

To fulfill *Althen* prong two, petitioner must show, by a preponderance of the evidence, "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. This prong is sometimes referred to as the "did it cause" test; i.e., in this particular case, did the vaccine(s) cause the alleged injury. *Broekelschen*, 618 F.3d at 1345.

Proof of *Althen* prong two requires a logical explanation as to how the vaccine did cause the injury in the petitioner. "'A logical sequence of cause and effect' means what it sounds like—the claimant's theory of cause and effect must be logical." *Capizzano*, 440 F.3d at 1326. The proof need not rise to the level of scientific certainty, but rather to the Vaccine Act's preponderance standard under the system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants.'" *Andreu*, 569 F.3d at 1378. A physician may rely on the close temporal proximity between a vaccination and an injury in concluding that there is a logical sequence of cause and effect between the vaccine and the injury. *Capizzano*, 440 F. 3d at 1326.

2. Discussion & Conclusion

Dr. Gans speculated that D.B.'s mother had endometriosis which was an autoimmune condition and therefore may have put D.B. in a higher risk category for developing an autoimmune condition himself. Dr. Gans also opined that D.B.'s pre-vaccination history of prolonged thrush suggested that his immune system was not responding optimally. Resp. Ex. D

at 3. While Dr. Gans's retrospective "unifying diagnosis" – in which she put together multiple factors such as the mother's possible autoimmune endometriosis, the dime-sized bruise and the longerthan expected thrush coupled with the knowledge of the ultimate diagnosis of Evans syndrome – is not unreasonable and may tend to show that the Evans syndrome was present prior to the vaccination, those factors were somewhat speculative and were otherwise explained by Dr. Foreman. Accordingly, I have not accorded that alternative diagnosis significant weight in coming to my conclusion in this case.

If petitioners' theory of bystander activation or epitope spreading appeared to be sufficiently reliable, then prong two, a logical sequence of cause and effect, likely would have been fulfilled. However, as I have concluded that the evidence was insufficient to satisfy prong one, there is no need to make further finding on this part of the *Althen* criteria.

C. *Althen* Prong Three

1. Legal Standard

Althen prong three requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 543 (2011), *recons. den'd after remand,* 105 Fed. Cl. 353 (2012), *aff'd mem.*, 2013 WL 1896173 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

2. Discussion & Conclusion

After careful consideration and review of the medical records as well as the mother's testimony (which I found to be credible, persuasive, and limited to her personal recollections), I conclude that D.B. did not have bruising on the ear three days post-vaccination. The medical records sometimes refer to a "mark" on the ear and also report a history of ear-pulling. Additionally, petitioners' expert hematologist Dr. Forman, who has clinical experience vaccinating young patients and was familiar with their common reactions to hepatitis B vaccine, opined that post-vaccination irritability could have led to this pulling of the ear, which could lead to some discoloration.

D.B. did have a bruise at the vaccination site three days afterwards. However, Dr. Forman opined that bruising at the vaccination site would be a common finding and not necessarily evidence of a platelet deficiency. As noted above, I found this opinion to be credible based on Dr. Forman's significant clinical experience vaccinating children and adults in various states of health and his comparison of this bruise to the later, more widespread bruising in D.B.

I also found credible the mother's recollection that the deeper, more widespread bruises on D.B.'s legs, which were consistent with her later understanding of Evans syndrome, began on March 12, 2009. The mother credibly related her observation of these first bruises to her first appearance in divorce court on that same day, which was tied to a significant change in her life.

Both Dr. Forman and Dr. Byers supported the onset as being on or about March 12 with the full presentation by March 15, 2009. and Dr. Gans agreed that the appearance of bruising and petechiae would appear quite quickly.

My post-hearing order provided: "The undersigned will find that March 12 was the first date of a visible presentation of Evans syndrome. This leaves open the issue of how long it would take to develop a sufficiently low platelet count to produce the level of bruising seen on March 12. However, the likelihood is that the undersigned would conclude that the timing was appropriate." Scheduling Order entered November 15, 2016 (ECF No. 85). As the experts tended to agree that the clinically evident signs of bruising and petechiae could occur quite quickly once the condition became operative, I think it is reasonable to conclude that an onset date of March 12, 2009, is reasonable.

Accordingly, I conclude that if petitioners had presented an acceptable theory to fulfill *Althen* prong one, they likely would have satisfied *Althen* prong three because the temporal relationship between the Hep B vaccination on March 4, 2009, and the onset of Evans syndrome approximately eight days later appears to be medically acceptable, at least in comparison to accepted time periods for autoimmune onset of other conditions.

V. CONCLUSION

I appreciate the frustration that D.B., his parents, and his treating physicians must feel in trying to manage this very rare disease with its elusive pathophysiology and inconsistent response to treatment. I have great sympathy for what they have experienced. I have also been frustrated in trying to understand the possible cause. However, after carefully reviewing the testimony and the submitted literature, I unfortunately must conclude that the state of knowledge about Evans syndrome is insufficient to be able to conclude that the hepatitis B vaccine played a causal role in D.B.'s condition and that the evidence presented by respondent through the testimony and the literature, in favor of an immune regulatory defect to explain the disease, more likely than not explains the condition. Therefore, petitioners have not established entitlement to compensation in the Vaccine Program and their claim must be and is **DISMISSED.** In the absence of a motion for review filed pursuant to RCFC Appendix B, the Clerk of the Court is directed to enter judgment forthwith.[67]

IT IS SO ORDERED.

s/Thomas L. Gowen
Thomas L. Gowen
Special Master

[67] Entry of judgment is expedited by each party's filing notice renouncing the right to seek review. Vaccine Rule 11(a).